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(54) Title: BOROPEPTIDE INHIBITORS OF THROMBIN WHICH CONTAIN A SUBSTITUTED PYRROLIDINE RING

(57) Abstract

This invention relates to the discovery of novel and useful α-amino acid analogs, and the pharmaceutically acceptable salts and prodrugs thereof, containing a disubstituted pyrrolidine ring conjugated to an α-amino acid, useful as inhibitors of thrombin.

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Title

Boropeptide Inhibitors of Thrombin which Contain a Substituted Pyrrolidine Ring

Field of the Invention

This invention relates to the discovery of novel and useful α-amino acid analogs, and the pharmaceutically acceptable salts or prodrugs thereof, as inhibitors of thrombin. These compounds contain a disubstituted- pyrrolidine ring conjugated to an α-amino acid functionalized with an electrophilic group such as boronic acids and their esters, α-perhaloketones and aldehydes.

Background of the Invention

Thrombin plays several critical roles in hemostasis, the normal physiological process by which bleeding from an injured blood vessel is arrested. Thrombin cleaves soluble fibrinogen to form insoluble fibrin in the last proteolytic step of both the extrinsic and intrinsic pathways of the coagulation cascade. Fibrin may be further insolubilized through crosslinking by the thrombin-activated enzyme, factor XIIIa. In addition, thrombin-induced activation of platelets leads to their aggregation and the secretion of additional factors that further accelerate creation of a hemostatic plug. Thrombin also potentiates its own production by the activation of factors V and VIII. Recent reviews of the roles of thrombin in coagulation have been reported by Fenton in *Ann. N. Y. Acad. Sci.* **485**, 5-15 (1986); and Fenton et al. in *Blood Coagulation and Fibrinolysis* **2**, 69-75 (1991).

Owing to its multiple roles in clot formation, inhibition of thrombin offers a therapeutic opportunity for development of anticoagulants useful in the treatment of thrombosis. Specific thrombin inhibitors are anticipated to exhibit few of the adverse side effects, such as bleeding and interpatient variability, caused by anticoagulants currently in clinical use (B. Furie and B. C. Furie, *The New England Journal of Medicine* **326**, 800-806 (1992)).

A number of naturally occurring thrombin inhibitors have been isolated. These include the marine sponge natural products *Theonella sp.* nazumamide A, a linear tetrapeptide reported by Fusetani et al., *Tetrahedron Lett.* **32**, 7073-4 (1991); *Theonella sp.* cyclotheonamides A and B reported by Fusenati et al., *J. Am. Chem. Soc.* **112**, 7053-4 (1990); and *Toxadocia cylindrica* toxadocial A, a sulfated C_{47} aldehyde reported by Nakao et al., *Tetrahedron Lett.* **34**, 1511-4 (1993). Hirudin, a 65 amino acid polypeptide, is responsible for the anticoagulant activity of the medicinal leech, *Hirudo medicinalis*. Recombinant versions of hirudin disclosed by Brauer et al. in AU-A-45977/85 and compounds incorporating hirudin fragments that have been disclosed by Maraganore et al. in PCT application WO91/02750; DiMaio et al., *J. Med. Chem.* **35**, 3331-3341 (1992); DiMaio and Konishi, PCT application WO91/19734; Witting et al., *Biochem. J.* **283**, 737-743 (1992); Krstenansky in European Patent Application EP 372 503 A2; may be clinically useful anticoagulants as suggested by Fareed et al., *Blood Coagulation and Fibrinolysis* **2**, 135-147 (1991).

Peptide analogs of thrombin substrates and reaction intermediates also inhibit thrombin. Examples of these include the tripeptide aldehyde (D)-Phe-Pro-Arg-H, disclosed by Bajusz et al., *Int. J. Peptide Protein Res.* **12**, 217-221 (1978); a chloromethyl ketone analog (Ac-

(D)-Phe-Pro-ArgCH_2Cl, disclosed by Kettner and Shaw, *Thromb. Res.* **14**, 969-73 (1979); polyfluorinated analogs such as (D)-Phe-Pro-Arg-CF_2-CF_3 disclosed by Kolb et al., AU-B-52881/86; Neises and Ganzhorn, European Patent Application EP 503 203 A1; Neises et al., European Patent Application EP 504 064 A1); and boronic acid analogs (Ac-(D)-Phe-Pro-boroArg, Kettner and Shenvi, European Patent Application EP 0 293 881 A2; Kettner et al., *J. Biol. Chem.* **265**, 18289-97 (1990). Borolysine, boroornithine and boroarginine inhibitors that contain various amino acid replacements have also been synthesized and shown to inhibit thrombin. Representative examples of these compounds include *t*-butyloxycarbonyl-(D)-trimethylsilylalanine-Pro-boroArg-pinanediol, disclosed in Metternich, European Patent Application EP 471 651 A2; Ac-(D)-β-napthylalanine-Pro-boroArg pinanediol ester, disclosed in Kakkar et al., PCT Application WO 92/07869; *N*-(*t*-butyloxycarbonyl)-(D)-phenylglycyl-(L)-prolyl-(L)-arginine aldehyde, disclosed in Gesellchen and Shuman, European Patent Application EP 0 479 489 A2 and *J. Med. Chem.* **36**, 314-319 (1993); and (HOOC-CH_2)$_2$-(L)-β-cyclohexylalanine-Pro-Arg-CH_2-O-CH_2-CF_3, disclosed by Atrash et al., European Patent Application EP 530 167 A1.

Numerous synthetic thrombin inhibitors, many of which incorporate an arginine or arginine mimic, have also been disclosed. These include arylsulfonylarginine amides such as (2*R*,4*R*)-1-[N^2-(3-ethyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-(L)-arginyl]-4-methyl-2-piperidinecarboxylate, disclosed by Okamoto et al., U.S. Patent No. 4,258,192; Okamoto et al., *Biochem. Biophys. Res. Commun.* **101**, 440-446 (1981); Kikumoto et al., *Biochemistry* **23**, 85-90 (1984); amidinophenylalanine derivatives such as (2-naphthylsulfonylglycyl)-4-amidino-phenylalanyl piperidine disclosed in Stüber and

Dickneite, European Patent Application EP 508 220; amino phenylalanine derivatives, disclosed in Okamoto et al., U.S. Patent No. 4,895,842; 1-[2-[5-(dimethylamino)naphth-1-ylsulfonamido]-3-(2-iminohexahydropyrimidin-5-yl)propanoyl]-4-methylpiperidine dihydrochloride, disclosed in Ishikawa et al., JP 88/227572 and JP 88/227573); and (*R*)-N-[(*RS*)-1-amidino-3-piperidinylmethyl]-α-(*o*-nitrobenzenesulfonamido)indole-3-propionamide, disclosed in Ackermann et al., European Patent Application EP 468 231). Isoquinolinyl guanidino benzoate derivatives, disclosed by Takeshita et al., European Patent Application EP 435 235 A1; and 2-[3-(4-amidinophenyl)]propionic acid derivatives, disclosed by Mack et al., PCT Application WO 93/01208 also act as thrombin inhibitors.

Many natural and synthetic thrombin inhibitors contain a 5-membered pyrrolidine ring. In most cases, the pyrrolidine ring is incorporated into the inhibitor as an integral component of the amino acid proline, a 2-substituted pyrrolidine, which in turn is bonded to the remaining atoms of the inhibitor via amide linkages. None of the cited references describe or suggest the new thrombin-inhibiting compounds of the present invention.

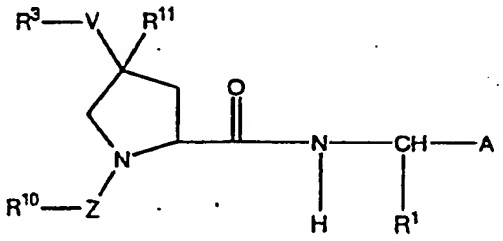
The novel compounds described in the present invention are substituted at the 4-position of the pyrrolidine ring. Although Winter et al., in European Patent Application WO 91/04247, have disclosed that 4-substituted-(L)-proline can mimic a dipeptide within a larger peptide or protein, and variably substituted prolines have been incorporated into compounds including bradykinin antagonists disclosed by Kyle et al., *J. Med. Chem.* **34**, 2649-2653 (1991); as well as vasopressin analogs Buku et al., *J. Med. Chem.* **30**, 1509-1512 (1987), no thrombin inhibitors containing a 5-membered

pyrrolidine ring substituted in the manner described here have been disclosed.

Despite considerable research in the area, more efficacious and specific thrombin inhibitors are needed as potentially valuable therapeutic agents for the treatment of thrombosis.

Summary of the Invention

[1] The present invention provides novel compounds of formula (I):



(I)

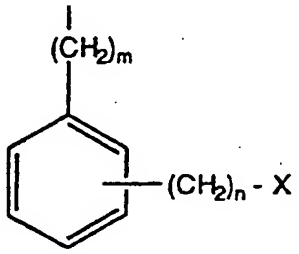
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is

a) $-(C_1-C_{12}$ alkyl$)-X$, or

b) $-(C_2-C_{12}$ alkenyl$)-X$, or

c)



X is

a) halogen,
b) $-CN$,
c) $-NO_2$,
d) $-CF_3$,
e) $-S(O)_pR^2$,
f) $-NHR^2$,
g) $-NHS(O)_pR^2$,
h) $-NHC(=NH)H$,
i) $-NHC(=NH)NHOH$,
j) $-NHC(=NH)NHCN$,
k) $-NHC(=NH)NHR^2$,
l) $-NHC(=NH)NHC(=O)R^2$,
m) $-C(=NH)H$,
n) $-C(=NH)NHR^2$,
o) $-C(=NH)NHC(=O)R^2$,
p) $-C(=O)NHR^2$,
q) $-C(=O)NHC(=O)R^2$,
r) $-C(=O)OR^2$,
s) $-OR^2$,
t) $-OC(=O)R^2$,
u) $-OC(=O)OR^2$,
v) $-OC(=O)NHR^2$,
w) $-OC(=O)NHC(=O)R^2$,
x) $-SC(=NH)NHR^2$;

R^2 is
a) hydrogen,
b) $-CF_3$
c) C_1-C_4 alkyl,
d) $-(CH_2)_q$-aryl;

R^3 and R^{10} are independently selected at each occurrence from the group consisting of:
a) hydrogen,
b) halogen,
c) $-(CR^6R^7)_tW(CR^8R^9)_u-R^9$,

d) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl,

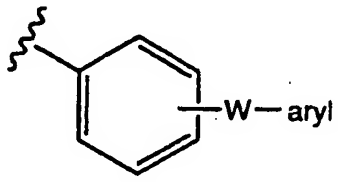
e) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl,

f) $-(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle,

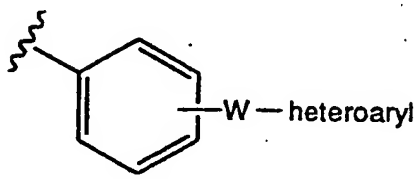
g) $-(CR^6R^7)_tW(CR^8R^9)_u$-adamantyl,

h) $-(CR^6R^7)_tW(CR^8R^9)_u(C_5-C_7)$cycloalkyl,

i)



j)



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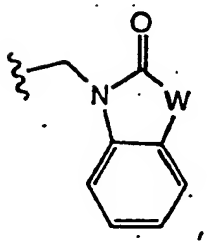

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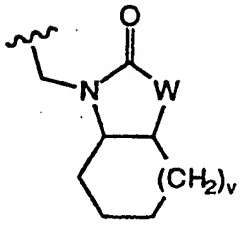

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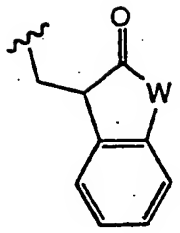

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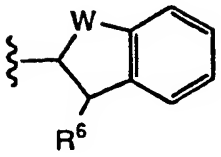

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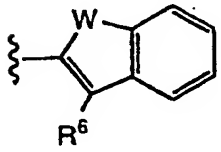

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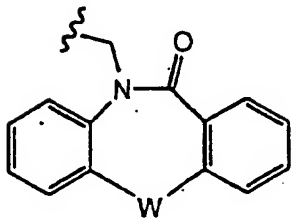

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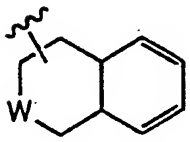

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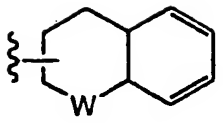
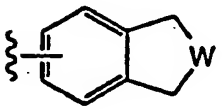


s)



;

R^3 and R^{10} when taken together form a ring such as:

a) $-(CR^6R^7)_t(CR^8R^9)_u-W-(CR^8R^9)_u(CR^6R^7)_t$;

b) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl-$(CR^8R^9)_uW(CR^6R^7)_t-$;

c) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl-$(CR^8R^9)_uW(CR^6R^7)_t-$;

d) $-(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle-$(CR^8R^9)_uW(CR^6R^7)_t-$;

e) $-(CR^6R^7)_tW(CR^8R^9)_u-W-(CR^8R^9)_u-W-(CR^6R^7)_t-$;

R^4 and R^5 are independently selected at each occurrence from the group consisting of:

a) hydrogen,

b) C_1-C_4 alkyl,

c) C_1-C_4 alkoxy,

d) C_5-C_7 cycloalkyl,

e) phenyl,

f) benzyl;

R^6, R^7, R^8 and R^9 are independently selected at each occurrence from the group consisting of:

a) hydrogen,

b) C_1-C_6 alkyl,

c) C_1-C_6 alkoxy,

d) C_3-C_8 cycloalkyl,

e) aryl,

f) heterocycle,

g) heteroaryl,

h) -W-aryl,

i) $-(CH_2)_wC(=O)OR^4$,

j) R^6 or R^7 can alternatively be taken together with R^6 or R^7 on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbons, or

k) R^8 or R^9 can alternatively be taken together with R^8 or R^9 on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbons;

R^{11} is

a) hydrogen,
b) C_1-C_4 alkyl,
c) C_1-C_4 thioalkyl,
d) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl,
e) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl,
f) $-(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle;
g) $-(CR^6R^7)_tW(CR^8R^9)_u-R^9$;

R^{11} and V, when taken together, can also be:

a) keto,
b) $=NR^{10}$,
c) $=C[(CR^6R^7)_tW(CR^8R^2)_uR^9]_2$;
d) $-(CR^6R^7)_tW(CR^8R^9)_uW-(CR^6R^7)_tW(CR^8R^9)_u-$

A is

a) $-BY^1Y^2$,
b) $-C(=O)CF_3$,
c) $-C(=O)CF_2CF_3$,
d) $-PO_3H_2$
d) $-C(=O)H$,
e) $-C(=O)$-1-piperdinyl,
f) $-C(=O)CH_2OCH_2CF_3$,
g) CH_2Cl
h) SO_2F;

Y^1 and Y^2 are

a) -OH,
b) -F,
c) $-NR^4R^5$ -,
d) $-C_1-C_8$ alkoxy, or;

when taken together Y^1 and Y^2 form:

e) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
f) a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
g) a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O;

W can be independently selected at each occurence from the group consisting of:

a) $-(CH_2)_x-$,
b) $-C(=O)-$,
c) $-C(=O)O-$,
d) $-C(=O)NR^4-$,
e) $-O-$,
f) $-OC(=O)-$,
g) $-OC(=O)O-$,
h) $-OC(=O)NR^4-$,
i) $-NR^4-$,
j) $-NR^4C(=O)-$,
k) $-NR^4C(=O)O-$,
l) $-NR^4C(=O)NR^5-$,
m) $-NR^4S(O)_p-$
n) $-S(O)_p-$,
o) $-S(O)_pO-$,
p) $-S(O)_pNR^4-$,

q) $-S(O)_pNR^4C(=O)-$,
r) $-S(O)_pNR^4C(=O)NR^5-$;

V is selected from the group consisting of:
a) $-(CH_2)_x-$,
b) $-(CH_2)_xC(=O)-$,
c) $-(CH_2)_xC(=O)O-$,
d) $-C(=O)(CH_2)_x-$,
e) $-O-(CH_2)_x-$,
f) $-O(CH_2)_xC(=O)-$,
g) $-O(CH_2)_xC(=O)O-$,
h) $-O(CH_2)_xC(=O)NR^4-$,
i) $-O(CH_2)_xS(O)_p-$,
j) $-(CH_2)_xS(O)_p-$,
k) $-(CH_2)_xS(O)_pO-$,
l) $-(CH_2)_xS(O)_pNR^4-$,
m) $-(CH_2)_xS(O)_pNR^4C(=O)-$,
n) $-(CH_2)_xS(O)_pNR^4C(=O)NR^5-$,
o) $-(CH_2)_xNR^4-$,
p) $-(CH_2)_xNR^4C(=O)-$,
q) $-(CH_2)_xNR^4C(=O)O-$,
r) $-(CH_2)_xNR^4C(=O)NR^5-$,
s) $-(CH_2)_xNR^4S(O)_p-$;

Z is selected from the group consisiting of:
a) $-(CH_2)_x-$,
b) $-(CH_2)_xC(=O)-$,
c) $-C(=O)(CH_2)_x-$,
d) $-(CH_2)_xC(=O)O-$,
e) $-(CH_2)_xC(=O)NR^4-$,
f) $-(CH_2)_xNR^4-$,
g) $-(CH_2)_xNR^4C(=O)-$,
h) $-(CH_2)_xNR^4C(=O)O-$,
i) $-(CH_2)_xNR^4C(=O)NR^5-$,
j) $-(CH_2)_xNR^4S(O)_p-$,

k) $-(CH_2)_xS(O)_p-$,

l) $-(CH_2)_xS(O)_pNR^4-$,

m can be 0 to 4;

n can be 0 to 4;

p can be 0 to 2

q can be 0 to 4;

r, s, t, u, and v are independently selected at each occurrence from 0 to 6,

w and x are independently selected at each occurence from 0 to 4;

with the following provisos:

(a) when V is $(CH_2)_x$, x cannot be 0 when R^3 is hydrogen;

(b) when Z is $-(CH_2)_xC(=O)-$ and $-C(=O)(CH_2)_x$ and x is 0, R^{10} cannot be halogen.

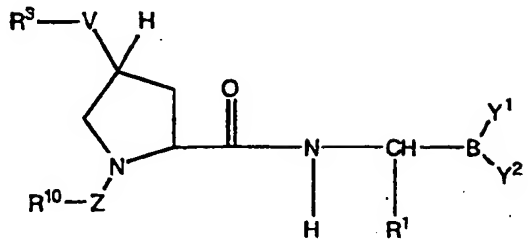
[2] Preferred compounds of formula (I) are those compounds wherein:

R^1 is (C_3-C_4 alkyl);

X is selected from the group consisting of:
$-NHC(=NH)H$, $-NHC(=NH)NHR^2$, $-NH_2$ or $-SC(=NH)NHR^2$;

R^2 is hydrogen or C_1-C_4 alkyl.

[3] More preferred compounds of formula (I) are compounds of formula (Ia):



(Ia)

or a pharmaceutically acceptable salts or prodrugs thereof, wherein:

R^1 is (C_3-C_4 alkyl);

X is selected from the group consisting of:
-NHC(=NH)H, -NHC(=NH)NHR^2, -NH_2 or -SC(=NH)NHR^2;

R^2 is hydrogen or C_1-C_4 alkyl;

R^3 and R^{10} are independently selected at each occurrence from the group consisting of:
a) hydrogen,
b) halogen,
c) $-(CR^6R^7)_tW(CR^8R^9)_u-R^9$
d) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl
e) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl;

R^4 and R^5 are independently selected at each occurrence from the group consisting of:
a) hydrogen,
b) C_1-C_4 alkyl,

c) C_1-C_4 alkoxy,
d) phenyl,
e) benzyl;

R^6, R^7, R^8, R^9 are independently selected at each occurrence from the group consisting of:
a) hydrogen
b) C_1-C_6 alkyl,
c) aryl,
d) $-(CH_2)_wC(=O)OR^4$, or;

Y^1 and Y^2 are
a) -OH,
b) -F,
c) $-NR^4R^5-$,
d) $-C_1$-C_8 alkoxy, or;

when taken together Y^1 and Y^2 form:
e) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
f) a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
g) a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O;

W can be independently selected at each occurrence from the group consisting of:
a) $-(CH_2)_x-$,
b) -O-,
c) $-S(O)_p-$,
d) $-NR^4-$,
e) $-NR^4C(=O)-$,

f) $-NR^4C(=O)O-$,

V is selected from the group consisting of:

a) $-(CH_2)_x-$,

b) $-O(CH_2)_x-$,

c) $-O(CH_2)_x(C=O)-$,

d) $-(CH_2)_xS(O)_p-$,

e) $-(CH_2)_xNR^4-$

f) $-(CH_2)_xNR^4C(=O)-$,

g) $-(CH_2)_xNR^4C(=O)O-$;

Z is selected from the group consisiting of:

a) $-(CH_2)_xC(=O)-$,

b) $-C(=O)(CH_2)_x-$,

c) $-(CH_2)_xC(=O)O-$,

p can be 0 or 2;

r can be independently selected at each occurrence from 0 to 3;

s can be independently selected at each occurrence from 0 to 3;

t can be independently selected at each occurrence from 0 to 2;

u can be independently selected at each occurrence from 0 to 2;

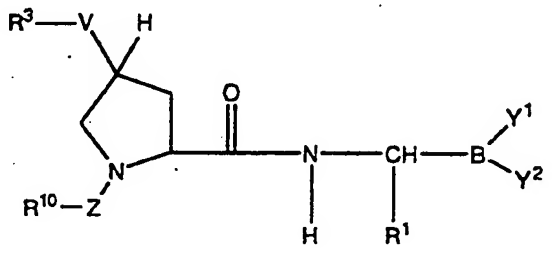
w can be independently selected at each occurrence from 0 to 2;

x can be independently selected at each occurrence from 0 to 3; with the following provisos:

(a) when V is $(CH_2)_x$, x cannot be 0 when R^3 is hydrogen;

(b) when Z is $-(CH_2)_xC(=O)-$ and $-C(=O)(CH_2)_x$ and x is 0, R^{10} cannot be halogen.

[4] Most preferred compounds of formula (I) are those compounds of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is (C_3-C_4 alkyl);

X is from the group consisting of $-NHC(=NH)H$, $-NHC(=NH)NHR^2$, $-NH_2$ or $-SC(=NH)NHR^2$;

R^2 is hydrogen or C_1-C_4 alkyl;

R^3 is independently selected from the group consisting of:
benzyl, phenyl, phenethyl, (3-phenyl)prop-1-yl, (2-methyl-1-phenyl)prop-2-yl, (2-methyl-2-phenyl)prop-1-yl, 1,1-diphenylmethyl, phenoxymethyl, phenylsulfonylmethyl, 2-(*m*-fluorophenyl)ethyl, 2-(3-pyridyl)ethyl, (*m*-aminophenyl)methyl, (*m*-

methylphenyl)methyl, (*p*-methylphenyl)methyl, 1-naphthylmethyl;

R^{10} is independently selected from the group consisting of:
methyl, *t*-butoxy, benzyloxy, phenethyl, benzyl, phenoxymethyl, isopropyl, isoamyl, *N*-methyl-*N*-*t*-butoxycarbonylaminomethyl, *N*-methylaminomethyl, (*m*-methyl) phenethyl, (*m*-fluoro) phenoxymethyl, (*m*-methyl) phenoxymethyl, (3-pyridyl) ethyl

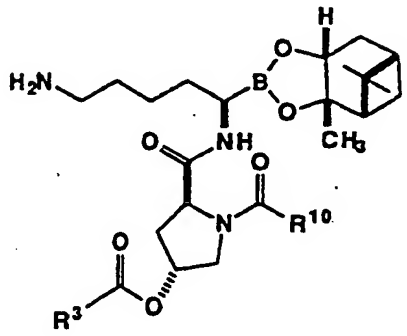
R^{11} is hydrogen;

Y^1 and Y^2 are
a) -OH,
b) -F,
c) $-NR^4R^5$ -,
d) $-C_1-C_8$ alkoxy, or;
when taken together Y^1 and Y^2 form:
e) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
f) a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,
g) a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O;

V is independently selected from the group consisting of:
O, -OC(=O)-, S, -NH-;

Z is -C(=O)-.

[5] Specifically preferred compounds of formula (I) are those compounds of formula (Ib):



(Ib)

selected from the list consisting of:

the compound of formula (Ib) wherein R^3 is phenyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 3-phenylprop-1-yl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 1,1-dimethyl-2-phenylethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 2,2-dimethyl-2-phenylethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is diphenylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenoxymethyl and R^{10} is methyl;

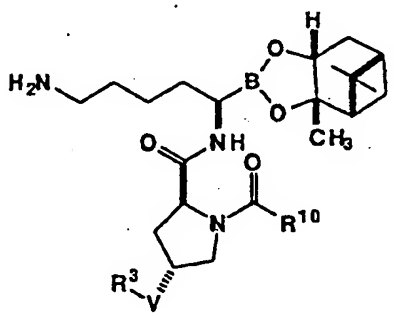
the compound of formula (Ib) wherein R^3 is phenylsulfonylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is (*m*-fluorophenyl)ethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is (3-pyridylethyl) and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenylethyl and R^{10} is phenethyl.

[6] Also specifically preferred compounds of formula (I) are those compounds of formula (Ic):



(Ic)

selected from the list consisting of:

the compound of formula (Ic) wherein V is sulfur, R^3 is phenyl and R^{10} is phenmethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is 3-phenylpropyl;

the compound of formula (Ic) wherein V is oxygen, (*m*-methyl)phenoxymethyl and R^{10} is 3-phenylpropyl;

the compound of formula (Ic) wherein V is oxygen, (*m*-fluoro)phenoxymethyl and R^{10} is 3-phenylpropyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-methylphenyl)ethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-fluoro)phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenoxymethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (*m*-fluorophenyl)methyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is amino, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is 2-propyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is isoamyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (*m*-methylphenyl)methyl and R^{10} is methyl;

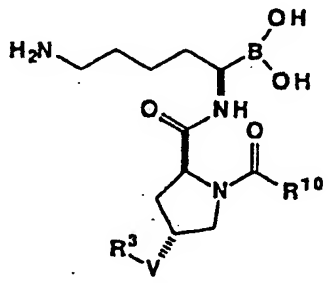
the compound of formula (Ic) wherein V is oxygen, R^3 is (*p*-methylphenyl)methyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (1-naphthyl)methyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is *N*-methyl-*N*-*t*-butoxycarbonylaminomethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is *N*-methylaminomethyl.

[7] Also specifically preferred compounds of formula (I) are those compounds of formula (Id):



(Ic)

selected from the list consisting of:

the compound of formula (Id) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Id) wherein V is oxygen, R^3 is (*m*-fluorophenyl)methyl and R^{10} is phenethyl.

the compound of formula (Id) wherein V is oxygen, R^3 is phenylmethyl and R^{10} (m-methyl)phenethyl;

Detailed Description of the Invention

The "(D)" prefix for the foregoing abbreviations indicates the amino acid is in the (D)-configuration. "D,L" indicates the amino acid is present as a mixture of the (D)- and the (L)-configuration. The prefix "boro" indicates amino acid residues where the carboxyl is replaced by a boronic acid or a boronic acid ester. For example, if R^1 is isopropyl and Y^1 and Y^2 are OH, the C-terminal residue is abbreviated "boroVal-OH" or "*boro*Valine" where "-OH" indicates the boronic acid is in the form of the free acid. The pinanediol boronic acid ester and the pinacol boronic acid ester are abbreviated "-$C_{10}H_{16}$" and "-C_6H_{12}", respectively. Examples of other useful diols for esterification with the boronic acids are 1,2-ethanediol, 1,3-propanediol, 1,2-propanediol, 2,3-butanediol, 1,2-diisopropylethanediol, 5,6-decanediol, and 1,2-dicyclohexylethanediol. Some common abbreviations used herein are: CBZ or Z, benzyloxycarbonyl; BSA, benzenesulfonic acid; THF, tetrahydrofuran; Boc-, t-butoxycarbonyl-; Ac-, acetyl; pNA, *p*-nitroaniline; DMAP, 4-dimethylaminopyridine; HOBT, 1-hydroxybenzotriazole and hydrate thereof; DCC, 1,3-dicyclohexylcarbodimide; Tris, Tris(hydroxymethyl)aminomethane; MS, mass spectrometry; FAB/MS, fast atom bombardment mass spectrometry. LRMS and HRMS are low and high resolution

mass spectrometry, respectively, using ammonia (NH_3-CI) or methane (CH_4-CI) as an ion source.

It is understood that many of the compounds of the present invention contain one or more chiral centers and that these stereoisomers may possess distinct physical and biological properties. The present invention comprises all of the stereoisomers or mixtures thereof. If the pure enantiomers or diasteromers are desired, they may be prepared using starting materials with the appropriate stereochemistry, or may be separated from mixtures of undesired stereoisomers by standard techniques, including chiral chromatography and recrystallization of diastereomeric salts.

When any variable (for example, R^1 through R^{10}, m, n, W, Z, etc.) occurs more than one time in any constituent or in formula (I), or any other formula herein, its definition on each occurrence is independent of its definition at every other occurrence.

In the instance that a subscript of a group is 0, it is intended to mean that the previous group is bonded directly with the next group in the sequence. For example, when:

R^3 is $-(CR^6R^7)_t-W-(CR^8R^9)_u$-aryl, and u is 0

it is the same as:

$$-(CR^6R^7)_t-W-\text{aryl}.$$

As described broadly above for R^6 and R^7, in the case "where R^6 (R^8) or R^7 (R^9) can alternatively be taken together with R^6 (R^8) or R^7 (R^9) on an adjacent carbon atom to form a direct bond", this can only occur when t (u) is greater than 1. The structure that would result from:

R^3 is $-(CR^6R^7)_t-W-(CR^8R^9)_u$-aryl, t = 2, u=2,

R^6 and R^7 are taken to for a double bond, and R^8 and R^9 taken to be a triple bond

would be:

$$-CR^6=CR^7-W-C\equiv C-\text{aryl}.$$

The term "amine-blocking group" or "amine-protecting group" as used herein, refers to various acyl, thioacyl, alkyl, sulfonyl, phosphoryl, and phosphinyl groups comprised of 1 to 20 carbon atoms. Substituents on these groups may include either alkyl, aryl and alkaryl which may contain the heteroatoms, O, S, and N as a substituent or as an inchain component. A number of amine-blocking groups are recognized by those skilled in the art of organic synthesis. Examples of suitable groups include formyl, acetyl, benzoyl, trifluoroacetyl, and methoxysuccinyl; aromatic urethane protecting groups, such as benzyloxycarbonyl; and aliphatic urethane protecting groups, such as *t*-butoxycarbonyl (also referred to as *t*-butyloxycarbonyl) or adamantyloxycarbonyl. Gross and Meienhofer, eds., *The Peptides*, Vol 3; 3-88 (1981), Academic Press, New York, and Greene and Wuts *Protective Groups in Organic Synthesis*, 315-405 (1991), J. Wiley and Sons, Inc., New York describe numerous suitable amine protecting groups and they are incorporated herein by reference for that purpose.

"Amino acid residues" as used herein, refers to natural or unnatural amino acid of either (D)- or (L)-configuration. Natural amino acids residues are Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. Roberts and Vellaccio, The Peptides, Vol 5; 341-449 (1983), Academic Press, New York, describe numerous suitable unnatural amino acids for use in this application and is incorporated herein by reference for that purpose.

"Amino acid residue" also refers to various amino acids where sidechain functional groups are coupled with appropriate protecting groups known to those skilled in the art. "The Peptides", Vol 3, 3-88 (1981) describes numerous suitable protecting groups and is incorporated herein by reference for that purpose.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- and polycyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and cyclooctyl, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo.

The term "aryl" is defined as phenyl, fluorenyl, biphenyl and naphthyl, which may be unsubstituted or include optional substitution with one to three substituents.

The term "heteroaryl" is meant to include 5-, 6- or 10-membered mono- or bicyclic aromatic rings which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S; said ring(s) may be unsubstituted or include optional substitution with one to three substituents. Included in the definition of the group heteroaryl, but not limited to, are the following: 2-, or 3-, or 4-pyridyl; 2-or 3-furyl; 2- or 3-benzofuranyl; 2-, or 3-thiophenyl; 2- or 3-benzo[b]thiophenyl; 2-, or 3-, or 4-quinolinyl; 1-, or 3-, or 4-isoquinolinyl; 2- or 3-pyrrolyl; 1- or 2- or 3-indolyl; 2-, or 4-, or 5-oxazolyl; 2-benzoxazolyl ; 2- or 4- or 5-imidazolyl; 1- or 2- benzimidazolyl; 2- or 4- or 5-thiazolyl; 2-benzothiazolyl; 3- or 4- or 5-isoxazolyl; 3- or 4- or 5-pyrazolyl; 3- or 4- or 5-isothiazolyl; 3- or 4-pyridazinyl; 2- or 4- or 5-pyrimidinyl; 2-pyrazinyl; 2-triazinyl; 3- or 4-

cinnolinyl; 1-phthalazinyl; 2- or 4-quinazolinyl; or 2-quinoxalinyl ring. Particularly preferred are 2-, 3-, or 4-pyridyl; 2-, or 3-furyl; 2-, or 3-thiophenyl; 2-, 3-, or 4-quinolinyl; or 1-, 3-, or 4-isoquinolinyl.

The term "heterocycle" is meant to include 5-, 6- or 10-membered mono- or bicyclic rings which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S; said ring(s) may be unsubstituted or include optional substitution with one to three substituents. Included in the definition of the group heterocycle, but not limited to, 2- or 3-pyrrolidinyl, a 2-, 3-, or 4-piperidinyl, or a 1-, 3-, or 4-tetrahdroisoquinolinyl, 1-, 2-, or 4-tetrahydroquinolinyl, 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothiophene, 1-, 2-, 3-, or 4-piperazinyl, and 1-, 2-, 3-, or 4-morpholino. Particularly preferred are 1-, 3-, or 4-tetrahdroisoquinolinyl, 2- or 3-pyrrolidinyl, and 2-, 3- or 4-piperidinyl.

The substituents that may be attached to the aryl, heteroaryl or heterocycle ring(s) may be independently selected at each occurrence from the group consisting of:

halogen, $-CF_3$, C_1-C_4 alkyl, nitro, phenyl, cyano,
$-(CH_2)_rR^4$, $-(CH_2)_rC(=O)(CH_2)_sR^4$,
$-(CH_2)_rC(=O)O(CH_2)_sR^4$,
$-(CH_2)_rC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$, methylenedioxy,
C_1-C_4 alkoxy, $-CH_2)_rO(CH_2)_sR^4$, $-(CH_2)_rOC(=O)(CH_2)_sR^4$,
$-(CH_2)_rOC(=O)O(CH_2)_sR^4$,
$-(CH_2)_rOC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$,
$-(CH_2)_rOC(=O)N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$,
$-(CH_2)_rS(O)_p(CH_2)_sR^4$, $-(CH_2)_rS(O)_p(CH_2)_sC(=O)R^4$,
$-(CH_2)_rS(O)_p(CH_2)_sC(=O)OR^4$,
$-(CH_2)_rS(O)_pN[(CH_2)_sR^4][(CH_2)_sR^5]$,
$-(CH_2)_rS(O)_pN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$,
$-(CH_2)_rN[(CH_2)_sR^4][(CH_2)_sR^5]$,

$-(CH_2)_rN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$,
$-(CH_2)_rN[(CH_2)_sR^4][C(=O)O(CH_2)_sR^5]$,
$-(CH_2)_rN[(CH_2)_sR^4]CON[(CH_2)_sR^4][(CH_2)_sR^5]$,
$-(CH_2)_rN[(CH_2)_sR^4]C(=O)-N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$,
$-(CH_2)_rN[(CH_2)_sR^4][S(O)_p(CH_2)_sR^5]$.

By "stable compound" or "stable structure" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture and formulation into an efficacious therapeutic agent.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of formula (I) is modified by making acid or base salts of the compound of formula (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, methanol, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the

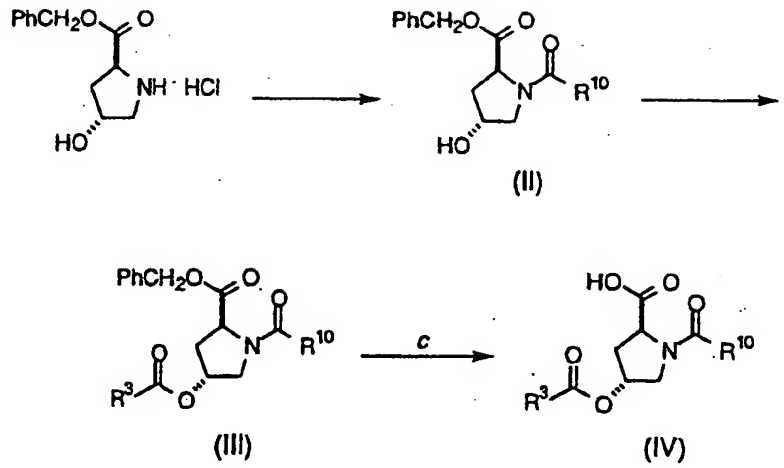
compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of formula (I) wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I).

Synthesis Discussion

Compounds of formula (I) can be prepared using the synthetic sequences that follow. The solvents employed are compatible with the reagents selected and the transformations being performed. It will be understood by those skilled in the art of organic synthesis that the order of the transformations proposed will be consistent with functionality present in the molecules and may require judgements during the selection of a procedure for preparation of a compound of the invention.

The general synthesis of *N*-acyl-4-(acyloxy)proline intermediates can be prepared by sequential acylations of the amine and hydroxyl functionalities and is shown in Scheme 1.

Scheme 1



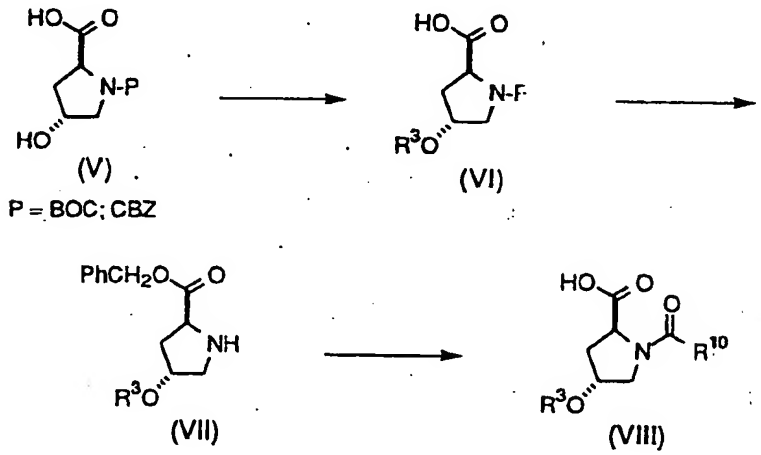
Thus, as an example, (L)-4-hydroxyproline benzyl ester hydrochloride, which is commercially available, or any other suitably protected hydroxyproline, can be treated with a trialkylamine base, typically 4-methylmorpholine, and an acid chloride ($R^{10}COCl$) to afford acylation product (II) selectively. The hydroxyl group can be converted to a corresponding ester by treatment with a second acid chloride (R^3COCl) in the presence of a trialkylamine or heterocyclic amine base, such as pyridine, and a suitable catalyst, such as but not limited to DMAP to generate (III). The carboxylic acid of the proline moiety can be liberated by hydrogenation using conditions reported by Hartney and Simonoff, *Org. React.* **VII**, 263 (1953) wherein an alcohol solution of the compound (III) may be affected under an atmosphere of hydrogen gas using a suitable catalyst, preferably platinum or palladium on carbon catalyst, to provide (IV).

One may vary the transformations indicated above depending upon the nature of the groups to be appended. One may employ alternative methods such as a mixed anhydride coupling, as reported by Anderson, et al. *J. Am. Chem. Soc.* **89**, 5012 (1967); or the DCC/HOBT protocol

described by König, and Geiger, *Chem. Ber.* **103**, 788 (1970) to form the requisite amide bond. Also, the DCC/DMAP esterification procedure, reported by Hassner, and Alexanian, *Tetrahedron Lett.* **19**, 4475 (1978) has proved useful for performing the second acylation reaction. Finally, one may choose an ester other than benzyl which might be removed hydrolytically or photilytically, such as photlytic deprotection. For example, with a methyl ester of (II), treatment of an alcoholic solution of the compound with a solution of sodium hydroxide so as to deliver 1 equivalent amount of NaOH followed by acidification should provide the carboxylic acid.

The *N*-acyl-4-(alkoxy)proline intermediates can prepared as shown in Scheme 2.

Scheme 2

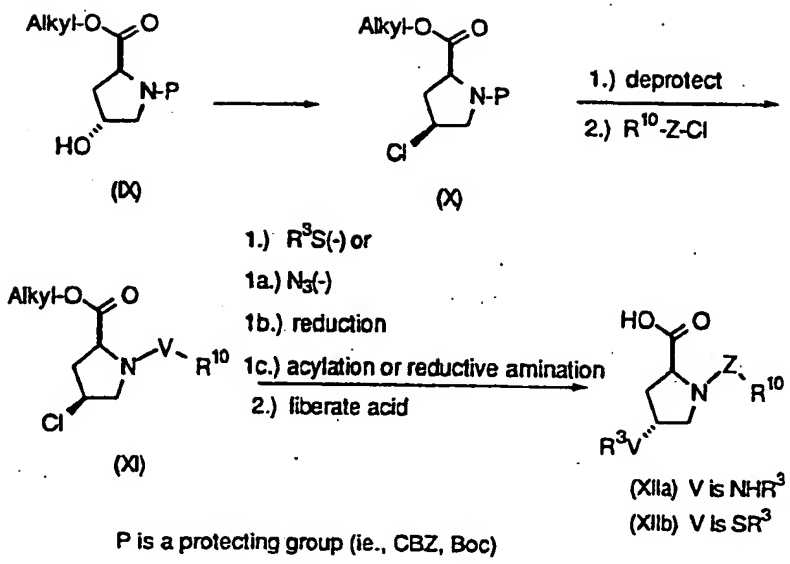


The hydroxyl function of an *N*-protected 4-hydroxyproline (V) can be alkylated according to the method of Smith et al., *J. Med. Chem.* **31**, 875 (1988), by treatment with an alkali metal hydride, such as but not limited to sodium hydride and an alkyl halide (R^3X) to give (VI). Removal

of the *N*-protecting group by an appropriate method know to one of skill in the art can provide (VII): the *t*-butyl carbamate can be cleaved upon treating with acid under anhydrous conditions; for example, trifluoroacetic acid in dichloromethane solution removes the *t*-butyl urethane of derivatives of (IV) at ambient temperature as reported by Bryan et. al., *J. Am. Chem. Soc.* **99**, 2353 (1977); alternatively anhydrous hydrogen chloride in dioxane may be used to prepare the HCl salt. Other methods for protection of the amine are delineated in Greene and Wuts (1991). The use of benzyl urethane is also viable where hydrogenation over palladium catalyst deliveres the free amine (VII). Acydlation by one of the methods discussed previously can provide (VIII).

The 4-amino and 4-mercaptoproline intermediates useful for the synthesis of compounds of the formula (I), wherein V is S, NH or derivatives thereof, can be prepared according to Scheme 3. The hydroxyproline ester (IX), wherein the amine is protected as the BOC or CBZ, can be reacted with carbon tetrachloride/ triphenylphosphine according to the method of Webb and Eigenbrot, *J. Org. Chem.*, **56**, 3009 (1991), to provide the chloride (X) with inversion of stereochemistry. The chloride can be displaced by a sulfur nucleophile, again with inversion of sterochemistry in a manner similar to that reported by Smith et al. (1988) to provide the displacement product (XIIb), sulfur-containing prolines. Similarly, the chloride can be displaced by sodium azide, which is reduced to the primary amine and converted by reductive amination to provide the displacement products (XIIa), nitrogen-containing prolines. The R^3 group in (XII) used in the displacement reaction need not be the ultimate R^3 of formula (I); methods for their removal are well known to those skilled in the art of organic synthesis. Methods for the attachment of preferred R^3 are described herein.

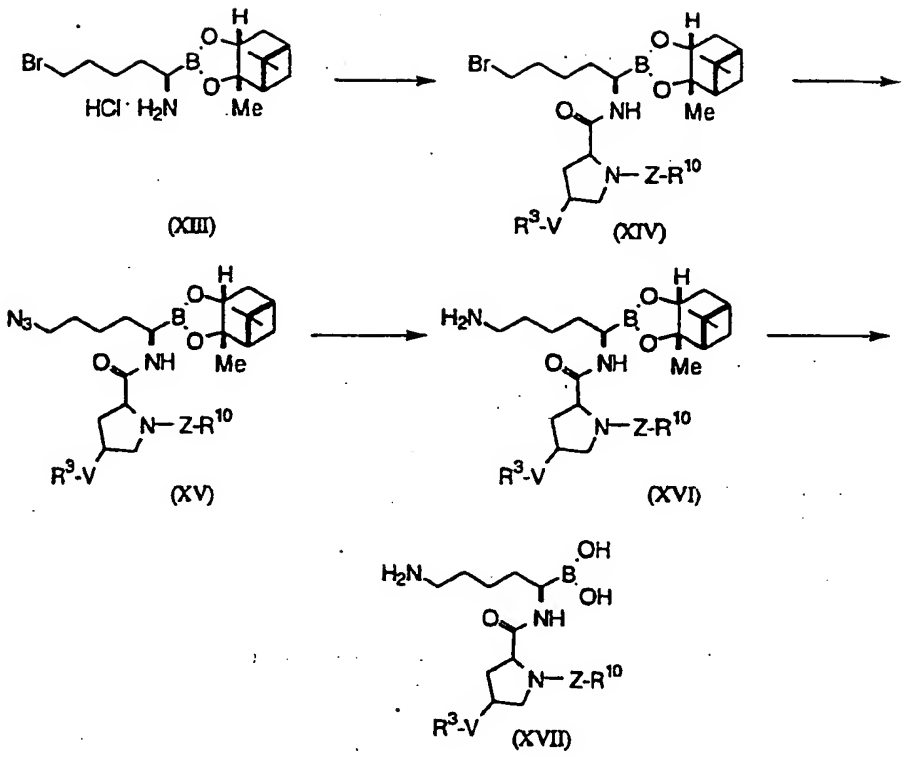
Scheme 3



These disubstituted prolines (XIIa,b) can be used in an analogous manner to that of (IV) or (VIII) described hereafter.

The construction of thrombin inhibitors of the present invention requires the coupling of either of the aforementioned intermediates, (IV), (VIII), or (XII) with a boron-containing fragment followed by manipulation of the pendant functionalities, as shown in Scheme 4.

Scheme 4



The synthesis of *boro*lysine-containing thrombin inhibitors (XVII) begins with the coupling of amine hydrochloride (XIII), disclosed by Kettner and Shenvi U.S. Patent No. 5.187.147, to provide amide (XIV). In practice, one may choose from several well-known methods to prepare (XIV) in suitably pure form, as purification of this intermediate is oftentimes impractical. One method calls for the combination of (XIII) and the acid chloride derived from (IV), (VIII) or (XII) in the presence of an amine base, such as but not limited to pyridine. Alternatively, one may employ either the mixed anhydride method, which involves mixing the acid to be coupled with an alkylchloroformate and an tertiary amine base, such as, but not limited to, *i*-butyl chloroformate and 4-methylmorpholine, followed by

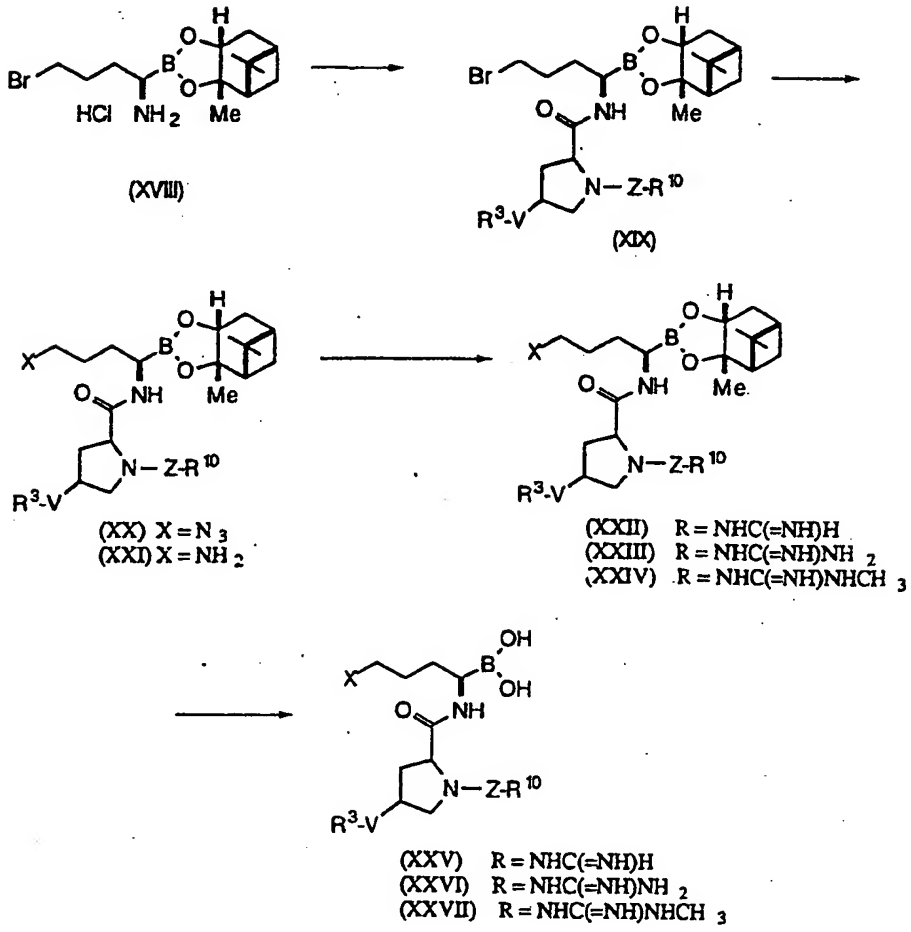
addition of the amine discussed previously, to prepare (XIV) from (IV), (VIII) or (XII); additionally the DCC/HOBT method may be used to access amines XIV and/or XII

Conversion of the bromide to the X group in R^1 of formula (I) can be accomplished by first reaction of bromide (X) with an inorganic azide, such as sodium or potassium azide, in an anhydrous polar aprotic solvent, such as acetone, *N,N*-dimethylformamide or methyl sulfoxide at temperatures ranging from ambient to 130°C; typically reaction with sodium azide in *N,N*-dimethylformamide at 65-70 °C for several hours provides (XV). Subsequent reduction of the azide function to the amine (XVI) is effected by catalytic hydrogenation of the azide in a solvent, such as an alcohol or ethyl acetate using a suitable transition metal catalyst under an atmosphere of hydrogen gas. Reduction of the azide (XX) in the presence of sulfur-containing prolines (XV, where V is S) can be done according to the method of Knowles et al., *Tetrahedron Lett.*, p. 3663 (1978) to provide the amines (XXI). A variety of alternative methods can be found in the monograph by Hudlicky, *Reductions In Organic Synthesis*, John Wiley and Sons, pp. 134 (1984). The amine (XVI) can be isolated as the free base or a salt, typically, but not exclusively hydrochloride or benzenesulfonate; other salts which impart improved physical properties may be preferred.

The method described by Matteson et al., *J. Am. Chem. Soc.* **102**, 7590 (1980) discloses a procedure for removing the pinanediol ester, however, the method employs reagents which may decompose the desired product. The preferred method for preparation of the free boronic acid (XVII) involves transesterification in the presence of excess phenylboric acid.

The amidine-type analogs, where the X group in R^1 of formula (I) is modified, can be prepared as shown in Scheme 5.

Scheme 5

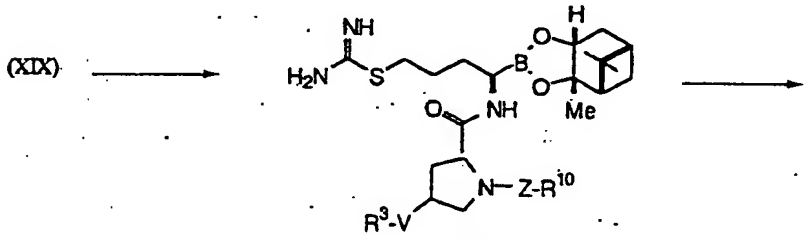


The guanidinium analogs can be prepared in a similar manner starting from amine hydrochloride (XVIII). Amide bond formation using one of the methods previously described provides (XIX), which can be converted to the azide (XX) by nucleophilic displacement of the bromide. Reduction of the azide using conditions already

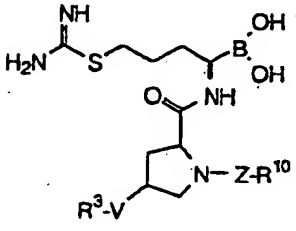
described can provide the amine (XXI). Preparation of formamidine (XXII) can be accomplished by reaction of amine (XXI) with ethyl formimidate hydrochloride in the presence of DMAP according to the method of Ohme and Schmitz, Angew, Chem mt. Ed 6,566 (1967). Elaboration of (XXI) to guanidine (XXIII) can be accomplished by reaction with formamidinesulfonic acid in the presence of DMAP, according to that described in Kim et al., *Tetrahedron Lett.* **29**, 3183 (1988), whereas the analogous *N*-methylguanidine (XXIV) can be produced when *N*-methyl-formamidinesulfonic acid is employed according to the method of Walter and Rauden, Liebig Ann. Chem. 722, 98(1969). As before, transesterification with phenylboric acid yields acids (XXV)-(XXVIII).

The compounds of formula (I), wherein X is isothiouronium can be prepared as shown in Scheme 6.

Scheme 6



(XXVIII)



(XXIX)

Starting from intermediate bromide (XIX), the X group in formula (I) can be introduced directly by displacement of the halide using thiourea as the nucleophilic species thereby providing boronic ester (XXVIII). As described previously, transesterification using phenylboric acid yields (XXIX).

Examples

Example 78

N^1-[(4*R*)-*N*-Acetyl-4-(3-phenylpropionyl)oxy-(L)-prolyl]-*R*-borolysine, (+)-pinanediol ester

Part A: To a solution of (4*R*)-4-hydroxy-(L)-proline benzyl ester hydrochloride (2.67 g, 1.04 mol) in dichloromethane (CH_2Cl_2, 50 mL) at 0 °C was added 4-methylmorpholine (2.50 mL, 2.28 mmol) followed by acetyl chloride (0.72 mL, 1.09 mmol). The reaction mixture was warmed to room temperature over 12 hours and ethyl acetate (EtOAc, ca. 200 mL) was added. The organic layer was washed with saturated aqueous sodium bicarbonate ($NaHCO_3$, 1 x 30 mL), water (H_2O, 1 x 30 mL), saturated aqueous sodium chloride (NaCl, 1 x 30 mL), dried over sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The resulting oil (1.94 g, 71% yield) solidified on standing at room temperature. A sample of (4*R*)-*N*-acetyl-4-hydroxy-(L)-proline benzyl ester was recrystallized from hexanes:EtOAc to give white plates, mp 99-102 °C (orthorhombic, $P2_12_12_1$, a = 9.216, b = 9.315, c 15.420 Å). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (comp, 5H), 5.17 (s, 2H), 4.63 (m, 1H), 3.79 (dd, *J*= 10.6,4.6 Hz, 1H), 3.50 (d, *J*= 10.6 Hz, 1H), 2.29 (d, *J*= 4.4 Hz, 1H), 2.24 (m, 1H), 2.11 (m, 1H), 2.09 (s, 3H); LRMS 264 (M+H, base), 281 ($M+NH_4$); Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.84; H, 6.41; N, 5.38.

Part B: To a solution of the product from Part A (370 mg, 1.41 mmol) and pyridine (0.17 mL, 2.10 mmol) in CH_2Cl_2 (14 mL) at 0 °C was added 3-phenylpropionyl chloride (0.23 mL, 1.55 mmol). The reaction mixture was warmed to room temperature over 3 hours and added to EtOAc (ca. 75 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (1 x 25 mL), half-saturated aqueous copper (II) sulfate (1 x 25 mL), sat. aq. NaCl (1 x 25 mL), dried (Na_2SO_4) and was concentrated under reduced pressure. The residue was purified by flash chromatography, elution with 2:1 EtOAc-hexanes to give (4*R*)-*N*-acetyl-4-(3-phenylpropionyl)oxy-(L)-proline benzyl ester (340 mg) as an oil in 61% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (comp, 5H), 7.28 (m, 2H), 7.19 (m, 3H), 5.30 (m, 1H), 5.18 (m, 2H), 4.51 (dd, *J*= 8.4, 8.0 Hz, 1H), 3.84 (dd, *J*= 11.7, 4.7 Hz, 1H), 3.46 (d, *J*= 11.7 Hz, 1H), 2.93 (t, *J*= 7.5 Hz, 2H), 2.64 (t, *J*= 7.5 Hz, 2H) 2.28 (m, 1H), 2.13 (m, 1H), 2.03 (s, 3H); LRMS 396 (M+H, base).

Part C: A solution of the product from Part B (340 mg, 0.86 mmol) together with palladium on charcoal (50 mg) in methanol (MeOH, 9 mL) was stirred under hydrogen (1 atm) for 2 hours. The reaction mixture was filtered through a pad of Celite with additional MeOH (ca. 10 mL) and the filtrate was concentrated under reduced pressure to give (4*R*)-*N*-acetyl-4-(3-phenylpropionyl)oxy-(L)-proline (245 mg) as a foam in 93% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (comp, 5H), 5.28 (m, 1H), 4.57 (t, *J*= 7.7 Hz, 1H), 4.38 (br s, 1H), 3.76 (dd, *J*= 11.9, 4.5 Hz, 1H), 3.49 (s, 1H), 2.95 (t, *J*= 7.3 Hz, 2H), 2.66 (t, *J*= 7.3 Hz, 2H), 2.56 (m, 1H), 2.26 (m, 1H), 2.07 (s, 3H); LRMS 306 (M+H), 173 (base).

Part D: To a solution of the product from Part C (240 mg, 0.79 mmol) and 4-methylmorpholine (0.26 mL, 2.36 mmol) in tetrahydrofuran (THF, 6 mL) at -20 °C was added *i*-butyl chloroformate (0.11 mL, 0.87 mmol) after which the reaction mixture was stirred for 2 minutes. A solution of (1R)-5-bromoaminopentane-1-boronic acid (+)-pinanediol ester (299 mg, 0.79 mmol) in *N,N*-dimethylformamide (DMF, 2 mL) was added, the reaction was stirred at -20 °C for 15 minutes and warmed to room temperature over 18 hours. The reaction mixture was poured into EtOAc (ca. 50 mL) and washed with H_2O (3 x 15 mL), and sat. aq. NaCl (1 x 15 mL) dried (Na_2SO_4) and concentrated under reduced pressure to give (1*R*)-5-bromo-[(4*R*)-*N*-acetyl-4-(3-phenylpropionyl)oxy-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester (475 mg) as an oil in 96% yield. LRMS 631,633 (M+H), 551 (base).

Part E: A mixture of the product from Part D (470 mg, 0.75 mmol) and sodium azide (NaN_3, 97 mg, 1.50 mmol) in DMF (8 mL) was heated at 65-70 °C for 4 hours. The mixture was poured into EtOAc (ca. 75 mL). and washed with H_2O (3 x 20 mL), sat. aq. NaCl (1 x 20 mL), dried (Na_2SO_4), and concentration under reduced pressure to give (1*R*)-5-azido-[(4*R*)-*N*-acetyl-4-(3-phenylpropionyl)oxy-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester. (403 mg) as an oil in 91% yield. LRMS 594 (M+H, base).

Part F: A solution of the product from Part E (388 mg, 0.65 mmol) in MeOH (7 mL) together with palladium hydroxide on charcoal (35 mg) was stirred under hydrogen (1 atm) for 3 hours. The reaction mixture was filtered through a pad of Celite with additional MeOH (ca. 10 mL) and the filtrate was concentrated under reduced pressure to give 320 mg of the title compound as a foam in 86%

yield. LRMS 568 (M + 1, base); HRMS Cacld for $C_{31}H_{47}BN_3O_6$: 568.3558. Found: 568.3558.

Example 154

N^1-[(4*R*)-*N*-(3-Phenylpropionyl)-4-(benzyl)oxy-(L)-prolyl]-*R*-borolysine, benzenesulfonate

To a mixture of Example 303 (1.95 g, 2.52 mmol) in H_2O (10 mL), Et_2O (15 mL), and sufficient MeOH (ca. 1.5 mL) to maintain a clear, biphasic system was added phenylboric acid (1.54 g, 12.6 mmol). The mixture was stirred for 14 hours, the layers were separated and the aqueous phase was extracted with Et_2O (5 x 20 mL). The aqueous layer was concentrated under reduced pressure to give the title compound (1.20 g) as an amorphous powder in 75% yield. LRMS 482 (M+H), 464 (base); HRMS Calcd for $C_{28}H_{39}BN_3O_5$ (ethylene gycol ester): 508.2983. Found: 508.2999.

Example 302

N^1-[(4*R*)-*N*-(3-Phenylpropionyl)-4-(phenyl)thio-(L)-prolyl]-*R*-borolysine (+)-pinanediol ester, hydrochloride

Part A: The commercially available starting material, (4*R*)-*N*-BOC-4-hydroxy-(L)-proline methyl ester was dissolved in CH_2Cl_2 (140 mL) and carbon tetrachloride (140 mL) and triphenylphosphine (42.56 g, 162.2 mmol) was added. The mixture was allowed to stir for 2 hours, ethanol (15 mL) was added and stirring was continued for an additional 16 hours. The mixture was concentrated under reduced pressure to 100 mL, cooled to -20 °C and Et_2O (200 mL) was added. The resulting precipitate was suction filtered and washed with Et_2O. The solid was further purified by flash chromatography, elution with

1:1 Et_2O-hexanes gave (4S)-*N*-BOC-4-chloro-(L)-proline methyl ester (17.03 g) as an oil in 84% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.37 (m, 2H), 3.95 (m, 1H), 3.75 (s, 3H), 3.63 (m, 1H), 2.63 (m, 1H), 2.38 (m, 1H), 1.45 (s, 9H).

Part B: A solution of the product from Part A (17.03 g, 64.5 mmol) in trifluoroacetic acid (20 mL) and CH_2Cl_2 (20 mL) was stirred 18 hours. The reaction mixture was concentrated under reduced pressure to give (4*S*)-4-chloro-(L)-proline methyl ester (18.05 g) as an oil in quanitative yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (comp, 2H), 3.87 (comp, 2H), 3.94 (s, 3H), 2.99 (m, 1H), 2.77 (m, 1H).

Part C: A solution of the product from Part B (30.28 g, 109 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and Et_3N (45.6 mL, 327 mmol) followed by hydrocinnamoyl chloride (17.8 mL, 120 mmol) were added slowly in order to maintain an internal temperature less than 10 °C. After stirring six hours, H_2O (50 mL) was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 (3 x 50 mL). The organics were washed with H_2O (25 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give (4*S*)-*N*-(3-phenylpropionyl)-4-chloro-(L)-proline methyl ester (17.44 g) as a waxy solid in 54% yield. LRMS 296.1 (base, M+H).

Part D: EtOH (50 mL) was cooled to 0 °C and sodium (0.78 g, 33.8 mmol) was added. After the hydrogen evolution ceased, thiophenol (3.72 g, 33.8 mmol) was added and the reaction mixture stirred for 15 minutes at 0 °C, and the product from Part C (5 g, 16.9 mmol) was added. The stirring was continued for an additional 16 hours at room temperature. The mixture was concentrated under reduced pressure, diluted with water (20 mL) and acidified with 1N HCl to pH 4. The aqueous solution was

extracted with EtOAc (3 x 30 mL), the organics dried with Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by flash chromatography, elution with chromatographed with 1:3 EtOAc-hexanes gave 2.06 g of (4*R*)-*N*-(3-phenylpropionyl)-4-(phenyl)thio-(L)-proline in 25% yield. LRMS 356.1 (M+H, base).

Part E: Using the method described above for the preparation of Example 78, Part D, (1*R*)-5-bromo-[(4*R*)-*N*-(3-phenylpropionyl)-4-(phenyl)thio-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester was isolated (2.43 g) as an oil in 85% yield. LRMS 681.2 683.2 (M+H, base).

Part F: Using the method described above for Example 78, Part E, the intermediate (1*R*)-5-azido-[(4*R*)-*N*-(3-phenylpropionyl)-4-(phenyl)thio-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester was isolated (2.42 g) as an oil in quantitative yield.

Part G: A solution of the product from Part F (2.42 g, 3.76 mmol) in 1,3-propanedithiol (1.62 g, 15 mmol), triethylamine (1.52 g, 15 mmol) and methanol (20 mL) was stirred at 50 °C for 24 hours. The reaction mixture was concentrated under reduce pressure and purified by flash chromatography through florosil, eluting with 1:9 MeOH-CH_2Cl_2. The concentrated residue was dissolved in diethyl ether (10 mL), acidified with 1 equivalent of 1N HCl in Et_2O and concentrated to give the title compound (0.73 g) as a solid in 31% yield. LRMS 617.3 (M+H, base). HRMS Cacld for $C_{35}H_{48}BN_3O_4S$: 617.34583. Found: 617.34580.

Example 303

N^1-[(4*R*)-*N*-(3-Phenylpropionyl)-4-(benzyl)oxy-(L)-prolyl]-*R*-borolysine, (+)-pinanediol ester

Part A: A solution of the commercially available starting material, (4*R*)-*N*-BOC-4-(benzyl)oxy-(L)-proline, previously reported by Smith et al., *J. Med. Chem.* **31**, 875 (1988); (2.11 g, 6.57 mmol), in CH_2Cl_2 (27 mL) was treated with anhydrous hydrogen chloride in dioxanes (4 M, 6.60 mL). The reaction mixture was stirred for 18 hours, during which time a white precipitate formed. The reaction was diluted with diethyl ether (Et_2O, ca. 100 mL) and the solid material was collected by suction filtration to afford (4*R*)-4-(benzyl)oxy-(L)-proline hydrochloride (1.60 g) as a white powder in 95% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 10.2 (br s, 1H), 7.36 (comp, 5H), 4.52 (s, 2H), 4.37 (dd, *J*= 10.8,7.5 Hz, 1H), 4.31 (m, 1H), 3.43 (dd, *J*= 12.5,4.4 Hz, 1H), 3.33 (d, *J*= 12.5 Hz, 1H), 2.48 (m, 1H), 2.11 (m, 1H); LRMS 222 (M+H, base).

Part B: A suspension of the product from Part A (1.50 g, 5.83 mmol) in CH_2Cl_2 (58 mL) at 0 °C was treated with 3-phenylpropionyl chloride (0.95 mL, 6.41 mmol) followed by 4-methylmorpholine (1.92 mL, 17.5 mmol). The reaction mixture was warmed to room temperature over 20 hours, treated with 2M aqueous hydrochloric acid (HCl) until pH = 2, and added to EtOAc (ca. 200 mL). The organic layer was washed with H_2O (3 x 50 mL), sat. aq. NaCl (1 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting solid was recrystallized from hexanes-EtOAc and gave a first crop (1.33 g, mp 127-129 °C) and a second crop (0.37 g, mp 122-125 °C) of (4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)oxy-(L)-proline as colorless plates in a total of 82% yield. (monoclinic, $P2_1$, a = 6.196, b = 9.101, c = 16.477Å, β = 98.98 °) ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (comp, 10H),

4.95 (br s, 1H), 4.69 (dd, J= 8.1,6.2 Hz, 1H), 4.50 (ABq, $\Delta\alpha_{AB}$ = 32.5 Hz, J_{AB}= 11.7 Hz, 2H), 4.20 (quin, J= 4.8 Hz, 1H), 3.46 (d, J= 4.8 Hz, 2H), 2.98 (t, J= 7.7 Hz, 2H), 2.59 (t, J= 7.4 Hz, 2H), 2.50 (m, 1H), 2.23 (ddd, J= 13.5, 8.4, 5.0 Hz, 1H); LRMS 354 (M+H, base); Anal. Calcd for $C_{21}H_{23}NO_4$: %C, 71.37; %H, 6.56; %N, 3.96. Found: %C, 71.39; %H, 6.57; %N, 3.92.

Part C: Using the method described above for the preparation of Example 78, Part D, (1*R*)-5-bromo-[(4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)oxy-(L)-prolyl]aminopentane-1-boronic acid (+)-pinanediol ester was isolated (2.80 g) as an oil in 90% yield. LRMS 679, 681 (M+H, base).

Part D: Using the method described above for Example 78, Part E, (1*R*)-5-azido-[(4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)oxy-(L)-prolyl]aminopentane-1-boronic acid (+)-pinanediol ester was isolated (2.31 g) as an oil in 94% yield. LRMS 642 (M+H, base).

Part E: A solution of product from Part D (2.24 g, 3.50 mmol) in MeOH (35 mL) together with palladium on charcoal (225 mg) was stirred under hydrogen (1 atm) for 1 hour. The reaction mixture was filtered through a pad of Celite with additional MeOH (ca. 30 mL) and the filtrate was concentrated under reduced pressure to give a foam which contained a small amount of unreacted azide. This material was resubjected to the hydrogenation conditions described above to afford the title compound (2.00 g) as a white foam in 93% yield. LRMS 616 (M+H, base).

Example 303a

N^1-[(4R)-*N*-(3-Phenylpropionyl)-4-(benzyl)oxy-(L)-prolyl]-*R*-borolysine, (+)-pinanediol ester, benzenesulfonate

A solution of Example 303 (2.00 g, 3.25 mmol) in methanol (25 mL) was treated with a solution of benzenesulfonic acid (0.514 g, 3.25 mmol) in methanol (8 mL). The mixture was allowed to stand at room temperature for 15 minutes and concentrated under reduced pressure to give a foam. The residue was washed with Et_2O (2 x 25 mL), which was decanted, then dissolved in EtOAc (ca. 20 mL) and triturated with Et_2O (ca. 75 mL) to afford an oily material which was washed with Et_2O (2 x 25 mL). The excess solvent was removed *in vacuo* to give the title compound (2.00 g) as a powder in 79% yield. LRMS 616 (M+H, base); HRMS Calcd for $C_{36}H_{51}BN_3O_5$: 616.3922. Found: 616.3921.

Example 375

N^1-[(4*R*)-*N*-(3-Phenylpropionyl)-4-(benzyl)amino-(L)-prolyl]-*R*-borolysine, (+)-pinanediol ester, hydrochloride

Part A: A mixture of the product from Example 302, Part C (3.00g, 10.1 mmol) and NaN_3 (3.30 g, 50.7 mmol) in DMF (15 mL) was heated to 75 °C for 18 hours. The reaction mixture was dissolved in H_2O (25 mL). The aqueous solution was extracted with Et_2O (3 x 25 mL), dried with $MgSO_4$ and concentrated to give (4*R*)-*N*-(3-phenylpropionyl)-4-azido-(L)-proline methyl ester (2.13 g) as an oil in 83% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (comp, 5H), 4.56 (m, 1H), 4.26 (m, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 3.40 (dd, J = 8, 2 Hz, 1H), 2.97 (m, 2H), 2,60 (m, 2H), 2.32 (comp, 2H). LRMS 303.1 (M+H, base).

Part B: Using the method described above for the preparation of Example 78, Part F, (4*R*)-*N*-(3-phenylpropionyl)-4-amino-(L)-proline methyl ester was isolated (2.43 g) as an oil in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (comp, 5H), 4.58 (m, 1H), 3.74 (m, 2H), 3.73 (s, 3H), 3.01 (m, 3H), 2.60 (m, 2H), 2.12 (m, 1H), 1.94 (m, 1H). LRMS 277.1 (M+H, base).

Part C: A mixture of the product from Part B (1.51 g, 5.46 mmol), benzaldehyde (0.58 g, 5.46 mmol), potassium acetate (0.54 g, 5.46 mmol) and 5% palladium on charcoal (0.21 g) was stirred in MeOH (25 mL) under hydrogen (3 atm) for 5 hours. The reaction mixture was filtered through a pad of Celite with additional MeOH (ca. 10 mL) and the filtrate concentrated under reduced pressure to give (4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)amino-(L)-proline methyl ester (2.00 g) as an oil in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (comp, 10H), 4.58 (m, 1H), 3.73 (comp, 4H), 3.50 (m, 1H), 3.44 (s, 3H), 3.15 (m, 1H), 2.96 (t, J = 7 Hz, 2H), 2.55 (m, 2H), 2.09 (m, 2H). LRMS 367.2 (M+H, base).

Part D: A solution of the product from Part C (2.00 g, 5.46 mmol) methanol (15 mL) and 1N sodium hydroxide (9 mL) was stirred for 24 hours. The pH of the solution was adjusted to 6 with 1N HCl and a white precipitate formed. The solid material was collected by suction filtration to give (4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)amino-(L)-proline (1.31 g) as a white powder in 68% yield. LRMS 353.2 (M+H, base).

Part E: Using the method described above for the preparation of Example 78, Part D, (1*R*)-5-bromo-[(4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)amino-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester was isolated (0.71 g) as an oil in 49% yield. LRMS 678.3 680.3 (M+H, base).

Part F: Using the method described above for Example 78, Part E, the intermediate (1*R*)-5-azido-[(4*R*)-*N*-(3-phenylpropionyl)-4-(benzyl)amino-(L)-prolyl]aminopentane-1-boronic acid, (+)-pinanediol ester was isolated (0.45 g) as an oil in 67% yield.

Part G: A solution of the product from Part F (0.45 g, 0.70 mmol) in MeOH (5 mL) together with 20% palladium hydroxide on charcoal (0.04 g) was stirred under hydrogen (1 atm) for 4 hours. The reaction mixture was filtered through a pad of Celite with EtOAc (ca. 10 mL). The filtrate was concentrated under reduced pressure and purified by flash chromatography through florosil, eluting with 1:9 MeOH-CH_2Cl_2. The concentrated residue was dissolved in Et_2O (10 mL), acidified with 2 equivalents of 1N HCl in Et_2O and concentrated to give the title compound (0.27 g) as a oil in 56% yield. LRMS 615.4 (M+H, base).

Example 1641

N^1-[(4*R*)-*N*-(Benzyloxy)carbonyl-4-(benzyl)oxy-(L)-prolyl]-*R*-borothioarginine, (+)-pinanediol ester

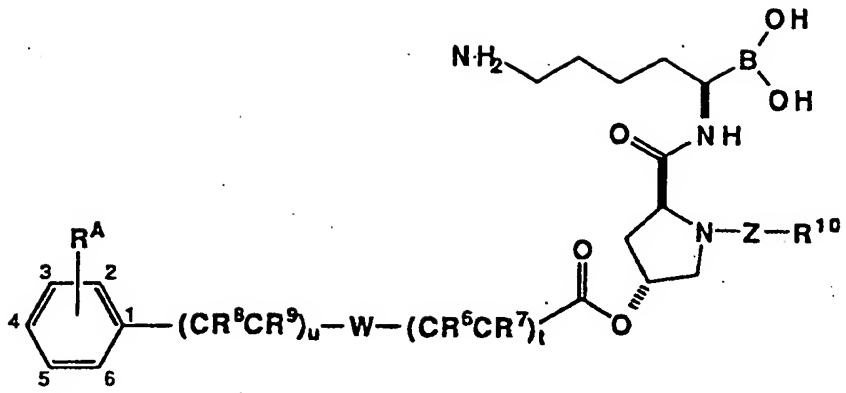
Part A: Using the method described above for Example 78, (1*R*)-4-bromo-[(4*R*)-*N*-(benzyloxy)carbonyl-4-(benzyl)oxy-(L)-prolyl]aminobutane-1-boronic acid, (+)-pinanediol ester (370 mg) was prepared as an oil in 99% yield. LRMS 667, 669 (M+H), 587 (base).

Part B: A mixture of the product from Part A (365 mg, 0.55 mmol) and thiourea (83 mg, 1.10 mmol) in ethanol (EtOH, 10 mL) was heated at reflux for 16 hours and cooled to room temperature. The reaction was poured into Et_2O (ca. 120 mL) and concentrated under reduced

pressure. The residue was triturated with Et_2O (ca. 50 mL), which was decanted. Purification of the residue by size exclusion chromatography on Sephadex LH-20, elution with MeOH, gave a glass which was dissolved in THF (1.5 mL) and treated with Et_2O (ca. 20 mL) to give a solid. The solid was washed with Et_2O (ca. 10 mL) and dried to afford the title compound (125 mg) as a white solid in 31% yield, mp 79-82 °C. LRMS 663 (M+H, base); HRMS Calcd for $C_{35}H_{48}BN_4O_6S$: 663.3388. Found: 663.3374.

Based on the representative examples detailed above, the following compounds of the invention can be prepared, as shown in Tables 1-20

Table 1

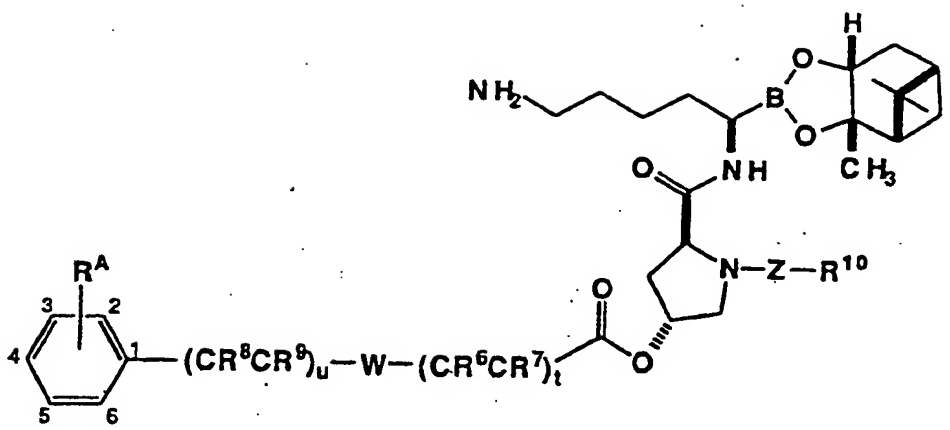


Ex.No	R^A	R^6	R^7	R^8	R^9	R^{10}	W	Z	t	u	Data
1	H	–	–	–	–	CH_3	–	CO	0	0	
2	H	–	–	–	–	CH_3	CH_2	CO	0	0	
3	H	H	H	–	–	CH_3	CH_2	CO	1	0	
4	H	H	H	H	H	CH_3	CH_2	CO	1	1	
5	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	
6	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	
7	H	–	–	Ph	H	CH_3	–	CO	0	1	
8	H	H	H	–	–	CH_3	O	CO	1	0	
9	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	
10	H	H	H	–	–	CH_3	SO_2	CO	1	0	
11	2-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
12	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
13	2, 3-diCH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
14	2-F	H	H	–	–	CH_3	CH_2	CO	1	0	
15	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	
16	4-F	H	H	–	–	CH_3	CH_2	CO	1	0	
17	2-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	
18	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	
19	2-NO_2	H	H	–	–	CH_3	CH_2	CO	1	0	
20	3-NO_2	H	H	–	–	CH_3	CH_2	CO	1	0	
21	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	

22	3-N	H	H	–	–	CH_3	CH_2	CO	1	0
23	4-N	H	H	–	–	CH_3	CH_2	CO	1	0
24	H	H	H	–	–	$(CH_2)_2Ph$	O	CO	1	0
25	H	CH_3	CH_3	–	–	$(CH_2)_2Ph$	O	CO	0	1
26	H	H	H	–	–	$(CH_2)_2Ph$	SO_2	CO	1	0
27	H	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
28	H	CH_3	CH_3	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
29	H	–	–	CH_3	CH_3	$(CH_2)_2Ph$	CH_2	CO	0	1
30	2-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
31	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
32	2, 3-diCH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
33	2-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
34	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
35	4-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
36	2-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
37	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
38	2-NO_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
39	3-NO_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
40	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
41	3-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
42	4-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0
43	H	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
44	H	CH_3	CH_3	–	–	CH_2Ph	CH_2	C(O)O	1	0
45	H	–	–	CH_3	CH_3	CH_2Ph	CH_2	C(O)O	0	1
46	2-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
47	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
48	2, 3-diCH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
49	2-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
50	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
51	4-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
52	2-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
53	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
54	2-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
55	3-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
56	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0

57	3-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
58	4-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
59	H	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
60	H	CH_3	CH_3	–	–	CH_2Ph	CH_2	C(O)NH	1	0
61	H	–	–	CH_3	CH_3	CH_2Ph	CH_2	C(O)NH	0	1
62	2-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
63	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
64	2, 3-diCH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
65	2-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
66	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
67	4-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
68	2-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
69	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
70	2-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
71	3-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
72	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
73	3-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
74	4-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
75	H	H	H	–	–	CH_2OPh	CH_2	CO	1	0

Table 2

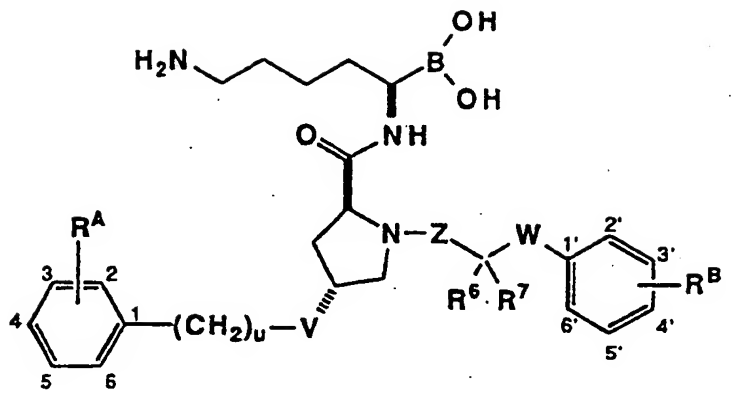


Ex.No	R^A	R^6	R^7	R^8	R^9	R^{10}	W	Z	t	u	Data
76	H	–	–	–	–	CH_3	–	CO	0	0	A
77	H	–	–	–	–	CH_3	CH_2	CO	0	0	B
78	H	H	H	–	–	CH_3	CH_2	CO	1	0	C
79	H	H	H	H	H	CH_3	CH_2	CO	1	1	D
80	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	E
81	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	F
82	H	–	–	Ph	H	CH_3	–	CO	0	1	G
83	H	H	H	–	–	CH_3	O	CO	1	0	H
84	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	
85	H	H	H	–	–	CH_3	SO_2	CO	1	0	I
86	2-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
87	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
88	2, 3-diCH_3	H	H	–	–	CH_3	CH_2	CO	1	0	
89	2-F	H	H	–	–	CH_3	CH_2	CO	1	0	
90	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	J
91	4-F	H	H	–	–	CH_3	CH_2	CO	1	0	
92	2-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	
93	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	
94	2-NO_2	H	H	–	–	CH_3	CH_2	CO	1	0	
95	3-NO_2	H	H	–	–	CH_3	CH_2	CO	1	0	
96	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	

97	3-N	H	H	–	–	CH_3	CH_2	CO	1	0	K
98	4-N	H	H	–	–	CH_3	CH_2	CO	1	0	
99	H	H	H	–	–	$(CH_2)_2Ph$	O	CO	1	0	
100	H	CH_3	CH_3	–	–	$(CH_2)_2Ph$	O	CO	0	1	
101	H	H	H	–	–	$(CH_2)_2Ph$	SO_2	CO	1	0	
102	H	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	L
103	H	CH_3	CH_3	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
114	H	–	–	CH_3	CH_3	$(CH_2)_2Ph$	CH_2	CO	0	1	
105	2-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
106	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
107	2, 3-diCH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
108	2-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
109	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
110	4-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
111	2-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
112	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
113	2-NO_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
114	3-NO_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
115	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
116	3-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
117	4-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	
118	H	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
119	H	CH_3	CH_3	–	–	CH_2Ph	CH_2	C(O)O	1	0	
120	H	–	–	CH_3	CH_3	CH_2Ph	CH_2	C(O)O	0	1	
121	2-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
122	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
123	2, 3-diCH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
124	2-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
125	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
126	4-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
127	2-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
128	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
129	2-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
130	3-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	
131	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	

132	3-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
133	4-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0
134	H	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
135	H	CH_3	CH_3	–	–	CH_2Ph	CH_2	C(O)NH	1	0
136	H	–	–	CH_3	CH_3	CH_2Ph	CH_2	C(O)NH	0	1
137	2-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
138	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
139	2, 3-diCH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
140	2-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
141	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
142	4-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
143	2-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
144	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
145	2-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
146	3-NO_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
147	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
148	3-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
149	4-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0
150	H	H	H	–	–	CH_2OPh	CH_2	CO	1	0

Table 3



Ex.No	R^A	R^B	R^6	R^7	Z	V	W	u	Data
151	H	H	H	H	C(O)O	O	–	1	
152	H	H	H	H	CO	O	CH_2	0	
153	H	H	CH_3	CH_3	CO	S	CH_2	0	
154	H	H	H	H	CO	O	CH_2	1	BSA salt,M
155	H	2'-CH_3	H	H	CO	O	CH_2	1	
156	H	3'-CH_3	H	H	CO	O	CH_2	1	N
157	H	2',3'-diCH_3	H	H	CO	O	CH_2	1	
158	H	2'-F	H	H	CO	O	CH_2	1	
159	H	3'-F	H	H	CO	O	CH_2	1	
160	H	2'-N	H	H	CO	O	CH_2	1	
161	H	3'-N	H	H	CO	O	CH_2	1	
162	3-CH_3	H	H	H	CO	O	CH_2	1	
163	3-CH_3	2'-CH_3	H	H	CO	O	CH_2	1	
164	3-CH_3	3'-CH_3	H	H	CO	O	CH_2	1	
165	3-CH_3	2',3'-diCH_3	H	H	CO	O	CH_2	1	
166	3-CH_3	2'-F	H	H	CO	O	CH_2	1	
167	3-CH_3	3'-F	H	H	CO	O	CH_2	1	
168	3-CH_3	2'-N	H	H	CO	O	CH_2	1	
169	3-CH_3	3'-N	H	H	CO	O	CH_2	1	
170	2-F	H	H	H	CO	O	CH_2	1	
171	2-F	2'-CH_3	H	H	CO	O	CH_2	1	

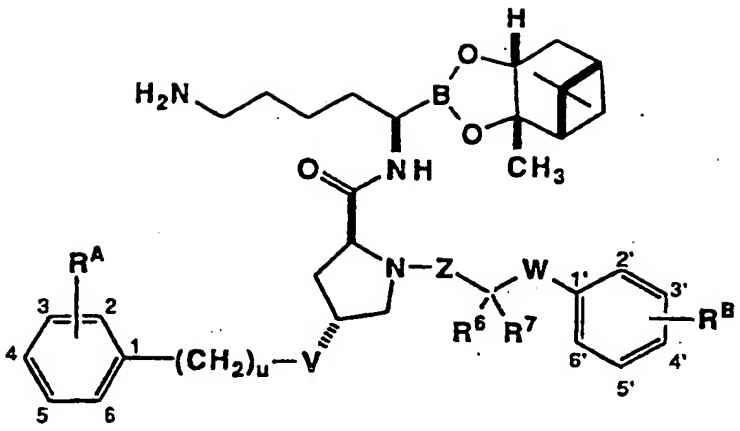
172	2-F	3'-CH_3	H	H	CO	O	CH_2	1	
173	2-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
174	2-F	2'-F	H	H	CO	O	CH_2	1	
175	2-F	3'-F	H	H	CO	O	CH_2	1	
176	2-F	2'-N	H	H	CO	O	CH_2	1	
177	2-F	3'-N	H	H	CO	O	CH_2	1	
178	3-F	H	H	H	CO	O	CH_2	1	O
179	3-F	2'-CH_3	H	H	CO	O	CH_2	1	
170	3-F	3'-CH_3	H	H	CO	O	CH_2	1	
181	3-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
182	3-F	2'-F	H	H	CO	O	CH_2	1	
183	3-F	3'-F	H	H	CO	O	CH_2	1	
184	3-F	2'-N	H	H	CO	O	CH_2	1	
185	3-F	3'-N	H	H	CO	O	CH_2	1	
186	3-NH_2	H	H	H	CO	O	CH_2	1	
187	3-NH_2	2'-CH_3	H	H	CO	O	CH_2	1	
188	3-NH_2	3'-CH_3	H	H	CO	O	CH_2	1	
189	3-NH_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
190	3-NH_2	2'-F	H	H	CO	O	CH_2	1	
191	3-NH_2	3'-F	H	H	CO	O	CH_2	1	
192	3-NH_2	2'-N	H	H	CO	O	CH_2	1	
193	3-NH_2	3'-N	H	H	CO	O	CH_2	1	
194	3-NO_2	H	H	H	CO	O	CH_2	1	
195	3-NO_2	2'-CH_3	H	H	CO	O	CH_2	1	
196	3-NO_2	3'-CH_3	H	H	CO	O	CH_2	1	
197	3-NO_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
198	3-NO_2	2'-F	H	H	CO	O	CH_2	1	
199	3-NO_2	3'-F	H	H	CO	O	CH_2	1	
200	3-NO_2	2'-N	H	H	CO	O	CH_2	1	
201	3-NO_2	3'-N	H	H	CO	O	CH_2	1	
202	2-N	H	H	H	CO	O	CH_2	1	
203	2-N	2'-CH_3	H	H	CO	O	CH_2	1	
204	2-N	3'-CH_3	H	H	CO	O	CH_2	1	
205	2-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
206	2-N	2'-F	H	H	CO	O	CH_2	1	

207	2-N	3'-F	H	H	CO	O	CH_2	1
208	2-N	2'-N	H	H	CO	O	CH_2	1
209	2-N	3'-N	H	H	CO	O	CH_2	1
210	3-N	H	H	H	CO	O	CH_2	1
211	3-N	2'-CH_3	H	H	CO	O	CH_2	1
212	3-N	3'-CH_3	H	H	CO	O	CH_2	1
213	3-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
214	3-N	2'-F	H	H	CO	O	CH_2	1
215	3-N	3'-F	H	H	CO	O	CH_2	1
216	3-N	2'-N	H	H	CO	O	CH_2	1
217	3-N	3'-N	H	H	CO	O	CH_2	1
218	4-N	H	H	H	CO	O	CH_2	1
219	4-N	2'-CH_3	H	H	CO	O	CH_2	1
220	4-N	3'-CH_3	H	H	CO	O	CH_2	1
221	4-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
222	4-N	2'-F	H	H	CO	O	CH_2	1
223	4-N	3'-F	H	H	CO	O	CH_2	1
224	4-N	2'-N	H	H	CO	O	CH_2	1
225	4-N	3'-N	H	H	CO	O	CH_2	1
226	H	H	H	H	CO	O	O	0
227	H	H	CH_3	CH_3	CO	S	O	0
228	H	H	H	H	CO	O	O	1
229	H	2'- CH_3	H	H	CO	O	O	1
230	H	3'-CH_3	H	H	CO	O	O	1
231	H	2', 3'-diCH_3	H	H	CO	O	O	1
232	H	2'-F	H	H	CO	O	O	1
233	H	3'-F	H	H	CO	O	O	1
234	H	2'-N	H	H	CO	O	O	1
235	H	3'-N	H	H	CO	O	O	1
236	3-CH_3	H	H	H	CO	O	O	1
237	3-CH_3	2'-CH_3	H	H	CO	O	O	1
238	3-CH_3	3'-CH_3	H	H	CO	O	O	1
239	3-CH_3	2', 3'-diCH_3	H	H	CO	O	O	1
240	3-CH_3	2'-F	H	H	CO	O	O	1
241	3-CH_3	3'-F	H	H	CO	O	O	1

242	3-CH_3	2'-N	H	H	CO	O	O	1
243	3-CH_3	3'-N	H	H	CO	O	O	1
244	2-F	H	H	H	CO	O	O	1
245	2-F	2'-CH_3	H	H	CO	O	O	1
246	2-F	3'-CH_3	H	H	CO	O	O	1
247	2-F	2', 3'-diCH_3	H	H	CO	O	O	1
248	2-F	2'-F	H	H	CO	O	O	1
249	2-F	3'-F	H	H	CO	O	O	1
250	2-F	2'-N	H	H	CO	O	O	1
251	2-F	3'-N	H	H	CO	O	O	1
252	3-F	H	H	H	CO	O	O	1
253	3-F	2'-CH_3	H	H	CO	O	O	1
254	3-F	3'-CH_3	H	H	CO	O	O	1
255	3-F	2', 3'-diCH_3	H	H	CO	O	O	1
256	3-F	2'-F	H	H	CO	O	O	1
257	3-F	3'-F	H	H	CO	O	O	1
258	3-F	2'-N	H	H	CO	O	O	1
259	3-F	3'-N	H	H	CO	O	O	1
260	3-NH_2	H	H	H	CO	O	O	1
261	3-NH_2	2'-CH_3	H	H	CO	O	O	1
262	3-NH_2	3'-CH_3	H	H	CO	O	O	1
263	3-NH_2	2', 3'-diCH_3	H	H	CO	O	O	1
264	3-NH_2	2'-F	H	H	CO	O	O	1
265	3-NH_2	3'-F	H	H	CO	O	O	1
266	3-NH_2	2'-N	H	H	CO	O	O	1
267	3-NH_2	3'-N	H	H	CO	O	O	1
268	3-NO_2	H	H	H	CO	O	O	1
269	3-NO_2	2'-CH_3	H	H	CO	O	O	1
270	3-NO_2	3'-CH_3	H	H	CO	O	O	1
271	3-NO_2	2', 3'-diCH_3	H	H	CO	O	O	1
272	3-NO_2	2'-F	H	H	CO	O	O	1
273	3-NO_2	3'-F	H	H	CO	O	O	1
274	3-NO_2	2'-N	H	H	CO	O	O	1
275	3-NO_2	3'-N	H	H	CO	O	O	1
276	2-N	H	H	H	CO	O	O	1

277	2-N	2'-CH_3	H	H	CO	O	O	1
278	2-N	3'-CH_3	H	H	CO	O	O	1
279	2-N	2', 3'-diCH_3	H	H	CO	O	O	1
280	2-N	2'-F	H	H	CO	O	O	1
281	2-N	3'-F	H	H	CO	O	O	1
282	2-N	2'-N	H	H	CO	O	O	1
283	2-N	3'-N	H	H	CO	O	O	1
284	3-N	H	H	H	CO	O	O	1
285	3-N	2'-CH_3	H	H	CO	O	O	1
286	3-N	3'-CH_3	H	H	CO	O	O	1
287	3-N	2', 3'-diCH_3	H	H	CO	O	O	1
288	3-N	2'-F	H	H	CO	O	O	1
289	3-N	3'-F	H	H	CO	O	O	1
290	3-N	2'-N	H	H	CO	O	O	1
291	3-N	3'-N	H	H	CO	O	O	1
292	4-N	H	H	H	CO	O	O	1
293	4-N	2'-CH_3	H	H	CO	O	O	1
294	4-N	3'-CH_3	H	H	CO	O	O	1
295	4-N	2', 3'-diCH_3	H	H	CO	O	O	1
296	4-N	2'-F	H	H	CO	O	O	1
297	4-N	3'-F	H	H	CO	O	O	1
298	4-N	2'-N	H	H	CO	O	O	1
299	4-N	3'-N	H	H	CO	O	O	1

Table 4



Ex.No	R^A	R^B	R^6	R^7	Z	V	W	u	Data
300	H	H	H	H	C(O)O	O	–	1	
301	H	H	H	H	CO	O	CH_2	0	
302	H	H	H	H	CO	S	CH_2	0	P
303	H	H	H	H	CO	O	CH_2	1	Q
303a	H	H	H	H	CO	O	CH_2	1	BSA salt
304	H	2'-CH_3	H	H	CO	O	CH_2	1	
305	H	3'-CH_3	H	H	CO	O	CH_2	1	R
306	H	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
307	H	2'-F	H	H	CO	O	CH_2	1	
308	H	3'-F	H	H	CO	O	CH_2	1	
309	H	2'-N	H	H	CO	O	CH_2	1	
310	H	3'-N	H	H	CO	O	CH_2	1	S
311	3-CH_3	H	H	H	CO	O	CH_2	1	
312	3-CH_3	2'-CH_3	H	H	CO	O	CH_2	1	
313	3-CH_3	3'-CH_3	H	H	CO	O	CH_2	1	
314	3-CH_3	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
315	3-CH_3	2'-F	H	H	CO	O	CH_2	1	
316	3-CH_3	3'-F	H	H	CO	O	CH_2	1	
317	3-CH_3	2'-N	H	H	CO	O	CH_2	1	
318	3-CH_3	3'-N	H	H	CO	O	CH_2	1	
319	2-F	H	H	H	CO	O	CH_2	1	

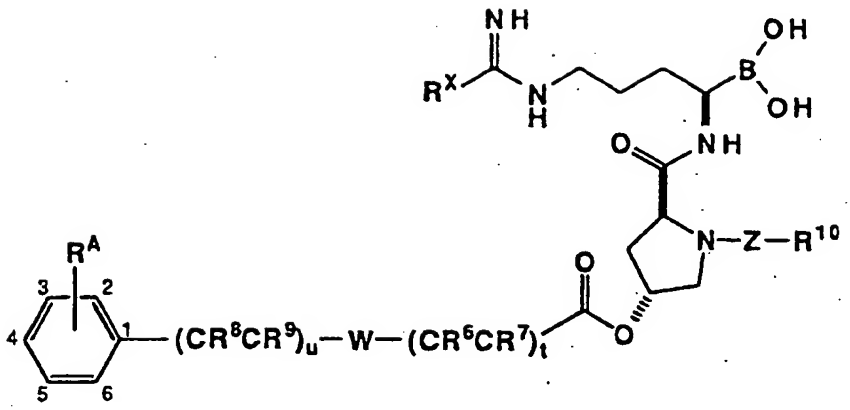
320	2-F	2'-CH_3	H	H	CO	O	CH_2	1	
321	2-F	3'-CH_3	H	H	CO	O	CH_2	1	
322	2-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
323	2-F	2'-F	H	H	CO	O	CH_2	1	
324	2-F	3'-F	H	H	CO	O	CH_2	1	
325	2-F	2'-N	H	H	CO	O	CH_2	1	
326	2-F	3'-N	H	H	CO	O	CH_2	1	
327	3-F	H	H	H	CO	O	CH_2	1	T
328	3-F	2'-CH_3	H	H	CO	O	CH_2	1	
329	3-F	3'-CH_3	H	H	CO	O	CH_2	1	
330	3-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
331	3-F	2'-F	H	H	CO	O	CH_2	1	
332	3-F	3'-F	H	H	CO	O	CH_2	1	
333	3-F	2'-N	H	H	CO	O	CH_2	1	
334	3-F	3'-N	H	H	CO	O	CH_2	1	
335	3-NH_2	H	H	H	CO	O	CH_2	1	U
336	3-NH_2	2'-CH_3	H	H	CO	O	CH_2	1	
337	3-NH_2	3'-CH_3	H	H	CO	O	CH_2	1	
338	3-NH_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
339	3-NH_2	2'-F	H	H	CO	O	CH_2	1	
340	3-NH_2	3'-F	H	H	CO	O	CH_2	1	
341	3-NH_2	2'-N	H	H	CO	O	CH_2	1	
342	3-NH_2	3'-N	H	H	CO	O	CH_2	1	
343	3-NO_2	H	H	H	CO	O	CH_2	1	
344	3-NO_2	2'-CH_3	H	H	CO	O	CH_2	1	
345	3-NO_2	3'-CH_3	H	H	CO	O	CH_2	1	
346	3-NO_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
347	3-NO_2	2'-F	H	H	CO	O	CH_2	1	
348	3-NO_2	3'-F	H	H	CO	O	CH_2	1	
349	3-NO_2	2'-N	H	H	CO	O	CH_2	1	
350	3-NO_2	3'-N	H	H	CO	O	CH_2	1	
351	2-N	H	H	H	CO	O	CH_2	1	
352	2-N	2'-CH_3	H	H	CO	O	CH_2	1	
353	2-N	3'-CH_3	H	H	CO	O	CH_2	1	
354	2-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	

355	2-N	2'-F	H	H	CO	O	CH_2	1	
356	2-N	3'-F	H	H	CO	O	CH_2	1	
357	2-N	2'-N	H	H	CO	O	CH_2	1	
358	2-N	3'-N	H	H	CO	O	CH_2	1	
359	3-N	H	H	H	CO	O	CH_2	1	
360	3-N	2'-CH_3	H	H	CO	O	CH_2	1	
361	3-N	3'-CH_3	H	H	CO	O	CH_2	1	
362	3-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
363	3-N	2'-F	H	H	CO	O	CH_2	1	
364	3-N	3'-F	H	H	CO	O	CH_2	1	
365	3-N	2'-N	H	H	CO	O	CH_2	1	
366	3-N	3'-N	H	H	CO	O	CH_2	1	
367	4-N	H	H	H	CO	O	CH_2	1	
368	4-N	2'-CH_3	H	H	CO	O	CH_2	1	
369	4-N	3'-CH_3	H	H	CO	O	CH_2	1	
370	4-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
371	4-N	2'-F	H	H	CO	O	CH_2	1	
372	4-N	3'-F	H	H	CO	O	CH_2	1	
373	4-N	2'-N	H	H	CO	O	CH_2	1	
374	4-N	3'-N	H	H	CO	O	CH_2	1	
375	H	H	H	H	CO	NH	CH_2	1	y
376	H	H	H	H	CO	O	(CH_2 CH_2)	1	K
377	H	H	H	H	CO	O	O	1	W
378	H	2'- CH_3	H	H	CO	O	O	1	
379	H	3'-CH_3	H	H	CO	O	O	1	X
380	H	2', 3'-diCH_3	H	H	CO	O	O	1	
381	H	2'-F	H	H	CO	O	O	1	
382	H	3'-F	H	H	CO	O	O	1	WW
383	H	2'-N	H	H	CO	O	O	1	
384	H	3'-N	H	H	CO	O	O	1	
385	3-CH_3	H	H	H	CO	O	O	1	
386	3-CH_3	2'-CH_3	H	H	CO	O	O	1	
387	3-CH_3	3'-CH_3	H	H	CO	O	O	1	
398	3-CH_3	2', 3'-diCH_3	H	H	CO	O	O	1	

399	3-CH_3	2'-F	H	H	CO	O	O	1
390	3-CH_3	3'-F	H	H	CO	O	O	1
391	3-CH_3	2'-N	H	H	CO	O	O	1
392	3-CH_3	3'-N	H	H	CO	O	O	1
393	2-F	H	H	H	CO	O	O	1
394	2-F	2'-CH_3	H	H	CO	O	O	1
395	2-F	3'-CH_3	H	H	CO	O	O	1
396	2-F	2', 3'-diCH_3	H	H	CO	O	O	1
397	2-F	2'-F	H	H	CO	O	O	1
398	2-F	3'-F	H	H	CO	O	O	1
399	2-F	2'-N	H	H	CO	O	O	1
400	2-F	3'-N	H	H	CO	O	O	1
401	3-F	H	H	H	CO	O	O	1
402	3-F	2'-CH_3	H	H	CO	O	O	1
403	3-F	3'-CH_3	H	H	CO	O	O	1
404	3-F	2', 3'-diCH_3	H	H	CO	O	O	1
405	3-F	2'-F	H	H	CO	O	O	1
406	3-F	3'-F	H	H	CO	O	O	1
407	3-F	2'-N	H	H	CO	O	O	1
408	3-F	3'-N	H	H	CO	O	O	1
409	3-NH_2	H	H	H	CO	O	O	1
410	3-NH_2	2'-CH_3	H	H	CO	O	O	1
411	3-NH_2	3'-CH_3	H	H	CO	O	O	1
412	3-NH_2	2', 3'-diCH_3	H	H	CO	O	O	1
413	3-NH_2	2'-F	H	H	CO	O	O	1
414	3-NH_2	3'-F	H	H	CO	O	O	1
415	3-NH_2	2'-N	H	H	CO	O	O	1
416	3-NH_2	3'-N	H	H	CO	O	O	1
417	3-NO_2	H	H	H	CO	O	O	1
418	3-NO_2	2'-CH_3	H	H	CO	O	O	1
419	3-NO_2	3'-CH_3	H	H	CO	O	O	1
420	3-NO_2	2', 3'-diCH_3	H	H	CO	O	O	1
421	3-NO_2	2'-F	H	H	CO	O	O	1
422	3-NO_2	3'-F	H	H	CO	O	O	1
423	3-NO_2	2'-N	H	H	CO	O	O	1

424	3-NO_2	3'-N	H	H	CO	O	O	1
425	2-N	H	H	H	CO	O	O	1
426	2-N	2'-CH_3	H	H	CO	O	O	1
427	2-N	3'-CH_3	H	H	CO	O	O	1
428	2-N	2', 3'-diCH_3	H	H	CO	O	O	1
429	2-N	2'-F	H	H	CO	O	O	1
430	2-N	3'-F	H	H	CO	O	O	1
431	2-N	2'-N	H	H	CO	O	O	1
432	2-N	3'-N	H	H	CO	O	O	1
433	3-N	H	H	H	CO	O	O	1
434	3-N	2'-CH_3	H	H	CO	O	O	1
435	3-N	3'-CH_3	H	H	CO	O	O	1
436	3-N	2', 3'-diCH_3	H	H	CO	O	O	1
437	3-N	2'-F	H	H	CO	O	O	1
438	3-N	3'-F	H	H	CO	O	O	1
439	3-N	2'-N	H	H	CO	O	O	1
440	3-N	3'-N	H	H	CO	O	O	1
441	4-N	H	H	H	CO	O	O	1
442	4-N	2'-CH_3	H	H	CO	O	O	1
443	4-N	3'-CH_3	H	H	CO	O	O	1
444	4-N	2', 3'-diCH_3	H	H	CO	O	O	1
445	4-N	2'-F	H	H	CO	O	O	1
446	4-N	3'-F	H	H	CO	O	O	1
447	4-N	2'-N	H	H	CO	O	O	1
448	4-N	3'-N	H	H	CO	O	O	1

Table 5

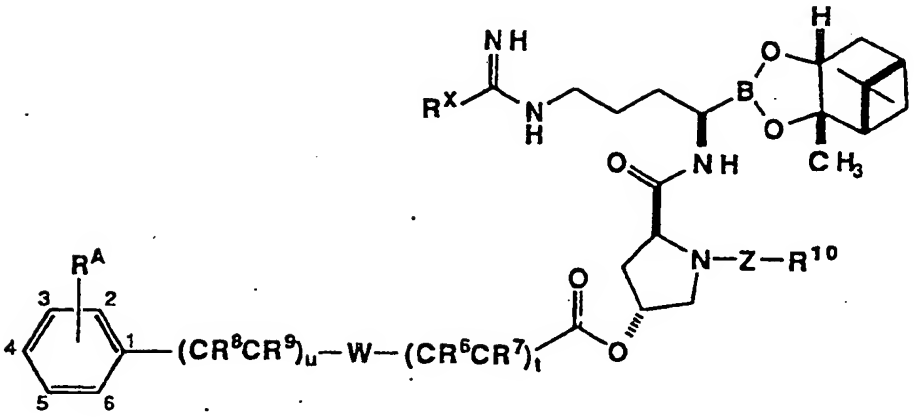


Ex.No	R^A	R^6	R^7	R^8	R^9	R^{10}	W	Z	t	u	R^X	Data
449	H	H	H	–	–	CH_3	CH_2	CO	1	0	H	
450	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	H	
451	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	H	
452	H	H	H	–	–	CH_3	O	CO	1	0	H	
453	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	H	
454	H	H	H	–	–	CH_3	SO_2	CO	1	0	H	
455	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	H	
456	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	H	
457	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	H	
458	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	H	
459	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H	
460	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H	
461	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H	
462	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H	
463	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H	
464	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H	
465	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H	
466	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H	
467	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H	
468	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H	
469	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H	
470	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H	
471	H	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N	

472	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	H_2N
473	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	H_2N
474	H	H	H	–	–	CH_3	O	CO	1	0	H_2N
475	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	H_2N
476	H	H	H	–	–	CH_3	SO_2	CO	1	0	H_2N
477	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
478	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
479	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
480	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
481	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
482	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
483	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
484	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
485	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
486	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
487	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
488	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
489	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
490	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
491	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
492	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
493	H	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
494	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	CH_3NH
495	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	CH_3NH
496	H	H	H	–	–	CH_3	O	CO	1	0	CH_3NH
497	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	CH_3NH
498	H	H	H	–	–	CH_3	SO_2	CO	1	0	CH_3NH
499	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
500	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
501	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
502	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
503	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
504	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
505	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
506	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH

507	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
508	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
509	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
510	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
511	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
512	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
513	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
514	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH

Table 6

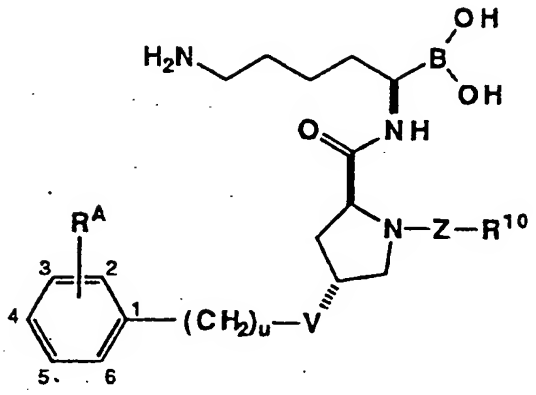


Ex.No	R^A	R^6	R^7	R^8	R^9	R^{10}	W	Z	t	u	R^X	Data
515	H	H	H	–	–	CH_3	CH_2	CO	1	0	H	
516	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	H	
517	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	H	
518	H	H	H	–	–	CH_3	O	CO	1	0	H	
519	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	H	
520	H	H	H	–	–	CH_3	SO_2	CO	1	0	H	
521	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	H	
522	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	H	
523	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	H	
524	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	H	
525	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H	

526	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H
527	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H
528	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H
529	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H
530	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H
531	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H
532	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H
533	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H
534	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H
535	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H
536	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H
537	H	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
538	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	H_2N
539	H	–	–	CH_3	CH_3	CH_3	CH_2	CO	0	1	H_2N
540	H	H	H	–	–	CH_3	O	CO	1	0	H_2N
541	H	CH_3	CH_3	–	–	CH_3	O	CO	1	0	H_2N
542	H	H	H	–	–	CH_3	SO_2	CO	1	0	H_2N
543	3-CH_3	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
544	3-F	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
545	3-NH_2	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
546	2-N	H	H	–	–	CH_3	CH_2	CO	1	0	H_2N
547	3-CH_3	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
548	3-F	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
549	3-NH_2	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
550	2-N	H	H	–	–	$(CH_2)_2Ph$	CH_2	CO	1	0	H_2N
551	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
552	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
553	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
554	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)O	1	0	H_2N
555	3-CH_3	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
556	3-F	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
557	3-NH_2	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
558	2-N	H	H	–	–	CH_2Ph	CH_2	C(O)NH	1	0	H_2N
559	H	H	H	–	–	CH_3	CH_2	CO	1	0	CH_3NH
560	H	CH_3	CH_3	–	–	CH_3	CH_2	CO	1	0	CH_3NH

561	H	-	-	CH_3	CH_3	CH_3	CH_2	CO	0	1	CH_3NH
562	H	H	H	-	-	CH_3	O	CO	1	0	CH_3NH
563	H	CH_3	CH_3	-	-	CH_3	O	CO	1	0	CH_3NH
564	H	H	H	-	-	CH_3	SO_2	CO	1	0	CH_3NH
565	3-CH_3	H	H	-	-	CH_3	CH_2	CO	1	0	CH_3NH
566	3-F	H	H	-	-	CH_3	CH_2	CO	1	0	CH_3NH
567	3-NH_2	H	H	-	-	CH_3	CH_2	CO	1	0	CH_3NH
568	2-N	H	H	-	-	CH_3	CH_2	CO	1	0	CH_3NH
569	3-CH_3	H	H	-	-	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
570	3-F	H	H	-	-	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
571	3-NH_2	H	H	-	-	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
572	2-N	H	H	-	-	$(CH_2)_2Ph$	CH_2	CO	1	0	CH_3NH
573	3-CH_3	H	H	-	-	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
574	3-F	H	H	-	-	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
575	3-NH_2	H	H	-	-	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
576	2-N	H	H	-	-	CH_2Ph	CH_2	C(O)O	1	0	CH_3NH
577	3-CH_3	H	H	-	-	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
578	3-F	H	H	-	-	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
579	3-NH_2	H	H	-	-	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH
580	2-N	H	H	-	-	CH_2Ph	CH_2	C(O)NH	1	0	CH_3NH

Table 7



Ex No.	R^A	R^{10}	Z	V	u	Data
581	H	CH_3	CO	O	0	
582	3-CH_3	CH_3	CO	O	0	
583	4-CH_3	CH_3	CO	O	0	
584	2-F	CH_3	CO	O	0	
585	3-F	CH_3	CO	O	0	
586	4-F	CH_3	CO	O	0	
587	3-NH_2	CH_3	CO	O	0	
588	4-NH_2	CH_3	CO	O	0	
589	3-NO_2	CH_3	CO	O	0	
590	4-NO_2	CH_3	CO	O	0	
591	3-N	CH_3	CO	O	0	
592	4-N	CH_3	CO	O	0	
593	H	CH_3	CO	S	0	
594	3-CH_3	CH_3	CO	S	0	
595	4-CH_3	CH_3	CO	S	0	
596	2-F	CH_3	CO	S	0	
597	3-F	CH_3	CO	S	0	
598	4-F	CH_3	CO	S	0	
599	3-NH_2	CH_3	CO	S	0	
600	4-NH_2	CH_3	CO	S	0	
601	3-NO_2	CH_3	CO	S	0	
602	4-NO_2	CH_3	CO	S	0	
603	3-N	CH_3	CO	S	0	
604	4-N	CH_3	CO	S	0	
605	H	$CH(CH_3)_2$	CO	O	0	
606	3-CH_3	$CH(CH_3)_2$	CO	O	0	
607	4-CH_3	$CH(CH_3)_2$	CO	O	0	
608	2-F	$CH(CH_3)_2$	CO	O	0	
609	3-F	$CH(CH_3)_2$	CO	O	0	
610	4-F	$CH(CH_3)_2$	CO	O	0	
611	3-NH_2	$CH(CH_3)_2$	CO	O	0	
612	4-NH_2	$CH(CH_3)_2$	CO	O	0	
613	3-NO_2	$CH(CH_3)_2$	CO	O	0	
614	4-NO_2	$CH(CH_3)_2$	CO	O	0	

615	3-N	$CH(CH_3)_2$	CO	O	0
616	4-N	$CH(CH_3)_2$	CO	O	0
617	H	$CH(CH_3)_2$	CO	S	0
618	3-CH_3	$CH(CH_3)_2$	CO	S	0
619	4-CH_3	$CH(CH_3)_2$	CO	S	0
620	2-F	$CH(CH_3)_2$	CO	S	0
621	3-F	$CH(CH_3)_2$	CO	S	0
622	4-F	$CH(CH_3)_2$	CO	S	0
623	3-NH_2	$CH(CH_3)_2$	CO	S	0
624	4-NH_2	$CH(CH_3)_2$	CO	S	0
625	3-NO_2	$CH(CH_3)_2$	CO	S	0
626	4-NO_2	$CH(CH_3)_2$	CO	S	0
627	3-N	$CH(CH_3)_2$	CO	S	0
628	4-N	$CH(CH_3)_2$	CO	S	0
629	H	$CH_2CH_2CH(CH_3)_2$	CO	O	0
630	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0
631	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0
632	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
633	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
634	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
635	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
636	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
637	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
638	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
639	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0
640	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0
641	H	$CH_2CH_2CH(CH_3)_2$	CO	S	0
642	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0
643	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0
644	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
645	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
646	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
647	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
648	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
649	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0

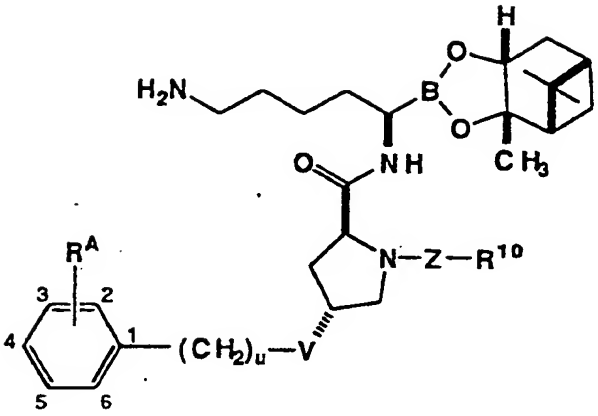
650	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
651	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
652	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
653	H	CH_3	CO	O	1
654	3-CH_3	CH_3	CO	O	1
655	4-CH_3	CH_3	CO	O	1
656	2-F	CH_3	CO	O	1
657	3-F	CH_3	CO	O	1
658	4-F	CH_3	CO	O	1
659	3-NH_2	CH_3	CO	O	1
660	4-NH_2	CH_3	CO	O	1
661	3-NO_2	CH_3	CO	O	1
662	4-NO_2	CH_3	CO	O	1
663	3-N	CH_3	CO	O	1
664	4-N	CH_3	CO	O	1
665	H	CH_3	CO	S	1
666	3-CH_3	CH_3	CO	S	1
667	4-CH_3	CH_3	CO	S	1
668	2-F	CH_3	CO	S	1
669	3-F	CH_3	CO	S	1
670	4-F	CH_3	CO	S	1
671	3-NH_2	CH_3	CO	S	1
672	4-NH_2	CH_3	CO	S	1
673	3-NO_2	CH_3	CO	S	1
674	4-NO_2	CH_3	CO	S	1
675	3-N	CH_3	CO	S	1
676	4-N	CH_3	CO	S	1
677	H	CH_3	CO	NH	1
678	3-CH_3	CH_3	CO	NH	1
679	4-CH_3	CH_3	CO	NH	1
680	2-F	CH_3	CO	NH	1
681	3-F	CH_3	CO	NH	1
682	4-F	CH_3	CO	NH	1
683	3-NH_2	CH_3	CO	NH	1
684	4-NH_2	CH_3	CO	NH	1

685	3-NO_2	CH_3	CO	NH	1
686	4-NO_2	CH_3	CO	NH	1
687	3-N	CH_3	CO	NH	1
688	4-N	CH_3	CO	NH	1
689	H	$CH(CH_3)_2$	CO	O	1
690	3-CH_3	$CH(CH_3)_2$	CO	O	1
691	4-CH_3	$CH(CH_3)_2$	CO	O	1
692	2-F	$CH(CH_3)_2$	CO	O	1
693	3-F	$CH(CH_3)_2$	CO	O	1
694	4-F	$CH(CH_3)_2$	CO	O	1
695	3-NH_2	$CH(CH_3)_2$	CO	O	1
696	4-NH_2	$CH(CH_3)_2$	CO	O	1
697	3-NO_2	$CH(CH_3)_2$	CO	O	1
698	4-NO_2	$CH(CH_3)_2$	CO	O	1
699	3-N	$CH(CH_3)_2$	CO	O	1
700	4-N	$CH(CH_3)_2$	CO	O	1
701	H	$CH(CH_3)_2$	CO	S	1
702	3-CH_3	$CH(CH_3)_2$	CO	S	1
703	4-CH_3	$CH(CH_3)_2$	CO	S	1
704	2-F	$CH(CH_3)_2$	CO	S	1
705	3-F	$CH(CH_3)_2$	CO	S	1
706	4-F	$CH(CH_3)_2$	CO	S	1
707	3-NH_2	$CH(CH_3)_2$	CO	S	1
708	4-NH_2	$CH(CH_3)_2$	CO	S	1
709	3-NO_2	$CH(CH_3)_2$	CO	S	1
710	4-NO_2	$CH(CH_3)_2$	CO	S	1
711	3-N	$CH(CH_3)_2$	CO	S	1
712	4-N	$CH(CH_3)_2$	CO	S	1
713	H	$CH(CH_3)_2$	CO	NH	1
714	3-CH_3	$CH(CH_3)_2$	CO	NH	1
715	4-CH_3	$CH(CH_3)_2$	CO	NH	1
716	2-F	$CH(CH_3)_2$	CO	NH	1
717	3-F	$CH(CH_3)_2$	CO	NH	1
718	4-F	$CH(CH_3)_2$	CO	NH	1
719	3-NH_2	$CH(CH_3)_2$	CO	NH	1

720	4-NH_2	$CH(CH_3)_2$	CO	NH	1
721	3-NO_2	$CH(CH_3)_2$	CO	NH	1
722	4-NO_2	$CH(CH_3)_2$	CO	NH	1
723	3-N	$CH(CH_3)_2$	CO	NH	1
724	4-N	$CH(CH_3)_2$	CO	NH	1
725	H	$CH_2CH_2CH(CH_3)_2$	CO	O	1
726	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
727	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
728	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
729	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
730	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
731	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
732	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
733	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
734	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
735	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
736	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
737	H	$CH_2CH_2CH(CH_3)_2$	CO	S	1
738	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
739	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
740	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
741	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
742	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
743	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
744	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
745	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
746	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
747	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
748	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
749	H	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
750	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
751	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
752	2-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
753	3-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
754	4-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1

755	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
756	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
757	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
758	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
759	3-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
760	4-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
761	H	$CH_2NH(CH_3)$	CO	O	1
762	H	$CH_2N(CH_3)CO_2C(CH_3)_3$	CO	O	1

Table 8



Ex. No.	R^A	R^{10}	Z	V	u	Data
763	H	CH_3	CO	O	0	
764	3-CH_3	CH_3	CO	O	0	
765	4-CH_3	CH_3	CO	O	0	
766	2-F	CH_3	CO	O	0	
767	3-F	CH_3	CO	O	0	
768	4-F	CH_3	CO	O	0	
769	3-NH_2	CH_3	CO	O	0	
770	4-NH_2	CH_3	CO	O	0	
771	3-NO_2	CH_3	CO	O	0	
772	4-NO_2	CH_3	CO	O	0	

773	3-N	CH_3	CO	O	0
774	4-N	CH_3	CO	O	0
775	H	CH_3	CO	S	0
776	3-CH_3	CH_3	CO	S	0
777	4-CH_3	CH_3	CO	S	0
778	2-F	CH_3	CO	S	0
779	3-F	CH_3	CO	S	0
780	4-F	CH_3	CO	S	0
781	3-NH_2	CH_3	CO	S	0
782	4-NH_2	CH_3	CO	S	0
783	3-NO_2	CH_3	CO	S	0
784	4-NO_2	CH_3	CO	S	0
785	3-N	CH_3	CO	S	0
786	4-N	CH_3	CO	S	0
787	H	$CH(CH_3)_2$	CO	O	0
788	3-CH_3	$CH(CH_3)_2$	CO	O	0
789	4-CH_3	$CH(CH_3)_2$	CO	O	0
790	2-F	$CH(CH_3)_2$	CO	O	0
791	3-F	$CH(CH_3)_2$	CO	O	0
792	4-F	$CH(CH_3)_2$	CO	O	0
793	3-NH_2	$CH(CH_3)_2$	CO	O	0
794	4-NH_2	$CH(CH_3)_2$	CO	O	0
795	3-NO_2	$CH(CH_3)_2$	CO	O	0
796	4-NO_2	$CH(CH_3)_2$	CO	O	0
797	3-N	$CH(CH_3)_2$	CO	O	0
798	4-N	$CH(CH_3)_2$	CO	O	0
799	H	$CH(CH_3)_2$	CO	S	0
800	3-CH_3	$CH(CH_3)_2$	CO	S	0
801	4-CH_3	$CH(CH_3)_2$	CO	S	0
802	2-F	$CH(CH_3)_2$	CO	S	0
803	3-F	$CH(CH_3)_2$	CO	S	0
804	4-F	$CH(CH_3)_2$	CO	S	0
805	3-NH_2	$CH(CH_3)_2$	CO	S	0
806	4-NH_2	$CH(CH_3)_2$	CO	S	0
807	3-NO_2	$CH(CH_3)_2$	CO	S	0

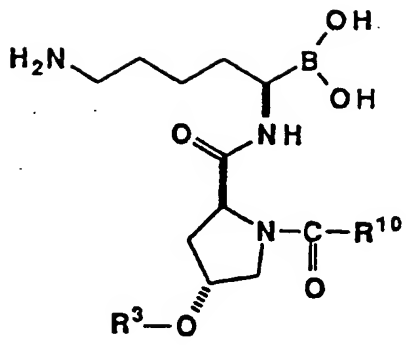
808	4-NO_2	$CH(CH_3)_2$	CO	S	0	
809	3-N	$CH(CH_3)_2$	CO	S	0	
810	4-N	$CH(CH_3)_2$	CO	S	0	
811	H	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
812	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
813	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
814	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
815	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
816	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
817	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
818	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
819	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
820	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
821	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
822	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0	
823	H	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
824	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
825	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
826	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
827	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
828	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
829	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
830	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
831	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
832	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
833	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
834	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0	
835	H	CH_3	CO	O	1	Z
836	3-CH_3	CH_3	CO	O	1	AA
837	4-CH_3	CH_3	CO	O	1	BB
838	2-F	CH_3	CO	O	1	
839	3-F	CH_3	CO	O	1	
840	4-F	CH_3	CO	O	1	
841	3-NH_2	CH_3	CO	O	1	
842	4-NH_2	CH_3	CO	O	1	

843	3-NO_2	CH_3	CO	O	1	
844	4-NO_2	CH_3	CO	O	1	
845	3-N	CH_3	CO	O	1	
846	4-N	CH_3	CO	O	1	
847	H	CH_3	CO	S	1	
848	3-CH_3	CH_3	CO	S	1	
849	4-CH_3	CH_3	CO	S	1	
850	2-F	CH_3	CO	S	1	
851	3-F	CH_3	CO	S	1	
852	4-F	CH_3	CO	S	1	
853	3-NH_2	CH_3	CO	S	1	
854	4-NH_2	CH_3	CO	S	1	
855	3-NO_2	CH_3	CO	S	1	
856	4-NO_2	CH_3	CO	S	1	
857	3-N	CH_3	CO	S	1	
858	4-N	CH_3	CO	S	1	
859	H	CH_3	CO	NH	1	
860	3-CH_3	CH_3	CO	NH	1	
861	4-CH_3	CH_3	CO	NH	1	
862	2-F	CH_3	CO	NH	1	
863	3-F	CH_3	CO	NH	1	
864	4-F	CH_3	CO	NH	1	
865	3-NH_2	CH_3	CO	NH	1	
866	4-NH_2	CH_3	CO	NH	1	
867	3-NO_2	CH_3	CO	NH	1	
868	4-NO_2	CH_3	CO	NH	1	
869	3-N	CH_3	CO	NH	1	
870	4-N	CH_3	CO	NH	1	
871	H	$CH(CH_3)_2$	CO	O	1	CC
872	3-CH_3	$CH(CH_3)_2$	CO	O	1	
873	4-CH_3	$CH(CH_3)_2$	CO	O	1	
874	2-F	$CH(CH_3)_2$	CO	O	1	
875	3-F	$CH(CH_3)_2$	CO	O	1	
876	4-F	$CH(CH_3)_2$	CO	O	1	
877	3-NH_2	$CH(CH_3)_2$	CO	O	1	

878	4-NH_2	$CH(CH_3)_2$	CO	O	1	
879	3-NO_2	$CH(CH_3)_2$	CO	O	1	
880	4-NO_2	$CH(CH_3)_2$	CO	O	1	
881	3-N	$CH(CH_3)_2$	CO	O	1	
882	4-N	$CH(CH_3)_2$	CO	O	1	
883	H	$CH(CH_3)_2$	CO	S	1	
884	3-CH_3	$CH(CH_3)_2$	CO	S	1	
885	4-CH_3	$CH(CH_3)_2$	CO	S	1	
886	2-F	$CH(CH_3)_2$	CO	S	1	
887	3-F	$CH(CH_3)_2$	CO	S	1	
888	4-F	$CH(CH_3)_2$	CO	S	1	
889	3-NH_2	$CH(CH_3)_2$	CO	S	1	
890	4-NH_2	$CH(CH_3)_2$	CO	S	1	
891	3-NO_2	$CH(CH_3)_2$	CO	S	1	
892	4-NO_2	$CH(CH_3)_2$	CO	S	1	
893	3-N	$CH(CH_3)_2$	CO	S	1	
894	4-N	$CH(CH_3)_2$	CO	S	1	
895	H	$CH(CH_3)_2$	CO	NH	1	
896	3-CH_3	$CH(CH_3)_2$	CO	NH	1	
897	4-CH_3	$CH(CH_3)_2$	CO	NH	1	
898	2-F	$CH(CH_3)_2$	CO	NH	1	
899	3-F	$CH(CH_3)_2$	CO	NH	1	
900	4-F	$CH(CH_3)_2$	CO	NH	1	
901	3-NH_2	$CH(CH_3)_2$	CO	NH	1	
902	4-NH_2	$CH(CH_3)_2$	CO	NH	1	
903	3-NO_2	$CH(CH_3)_2$	CO	NH	1	
904	4-NO_2	$CH(CH_3)_2$	CO	NH	1	
905	3-N	$CH(CH_3)_2$	CO	NH	1	
906	4-N	$CH(CH_3)_2$	CO	NH	1	
907	H	$CH_2CH_2CH(CH_3)_2$	CO	O	1	DD
908	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
909	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
910	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
911	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
912	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1	

913	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
914	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
915	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
916	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
917	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
918	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1	
919	H	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
920	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
921	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
922	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
923	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
924	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
925	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
926	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
927	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
928	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
929	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
930	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1	
931	H	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
932	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
933	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
934	2-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
935	3-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
936	4-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
937	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
938	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
939	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
940	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
941	3-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
942	4-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1	
943	H	$CH_2NH(CH_3)$	CO	O	1	EE
944	H	$CH_2N(CH_3)CO_2C(CH_3)_3$	CO	O	1	FF

Table 9



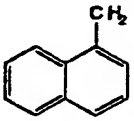
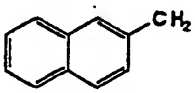
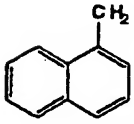
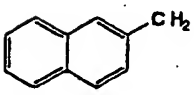
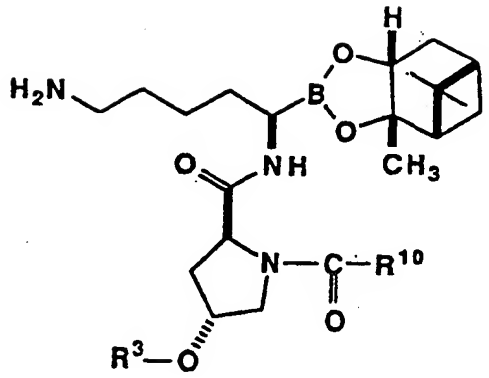
Ex No.	R^3	R^{10}	Data
945	CH_3	CH_3	
946	$(H_3C)_3C$	CH_3	
947		CH_3	
948		CH_3	
949	CH_3	CH_2CH_2Ph	
950	$(H_3C)_3C$	CH_2CH_2Ph	
951		CH_2CH_2Ph	
952		CH_2CH_2Ph	

Table 10



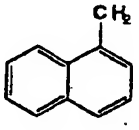
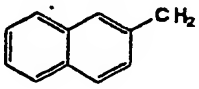
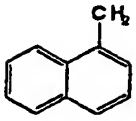
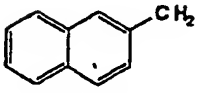
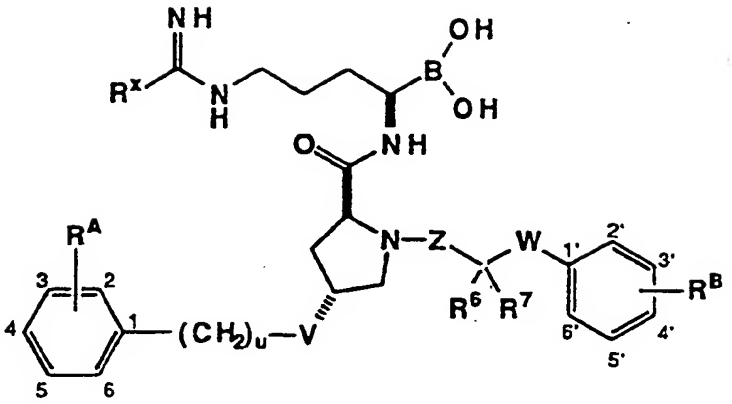
Ex No.	R^3	R^{10}	Data
953	CH_3	CH_3	
954	$(H_3C)_3C$	CH_3	GG
955		CH_3	HH
956		CH_3	
957	CH_3	CH_2CH_2Ph	
958	$(H_3C)_3C$	CH_2CH_2Ph	II
959		CH_2CH_2Ph	JJ
960		CH_2CH_2Ph	

Table 11



$R^x = H_2N$

ExNo.	R^A	R^B	R^6	R^7	Z	V	W	u	Data
961	H	H	H	H	C(O)O	O	–	1	
962	H	H	H	H	CO	O	CH_2	0	
963	H	H	H	H	CO	S	CH_2	0	
964	H	H	H	H	CO	O	CH_2	1	
965	H	2'- CH_3	H	H	CO	O	CH_2	1	
966	H	3'-CH_3	H	H	CO	O	CH_2	1	
967	H	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
968	H	2'-F	H	H	CO	O	CH_2	1	
969	H	3'-F	H	H	CO	O	CH_2	1	
970	H	2'-N	H	H	CO	O	CH_2	1	
971	H	3'-N	H	H	CO	O	CH_2	1	
972	3-CH_3	H	H	H	CO	O	CH_2	1	
973	3-CH_3	2'-CH_3	H	H	CO	O	CH_2	1	
974	3-CH_3	3'-CH_3	H	H	CO	O	CH_2	1	
975	3-CH_3	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
976	3-CH_3	2'-F	H	H	CO	O	CH_2	1	
977	3-CH_3	3'-F	H	H	CO	O	CH_2	1	
978	3-CH_3	2'-N	H	H	CO	O	CH_2	1	
979	3-CH_3	3'-N	H	H	CO	O	CH_2	1	
980	2-F	H	H	H	CO	O	CH_2	1	

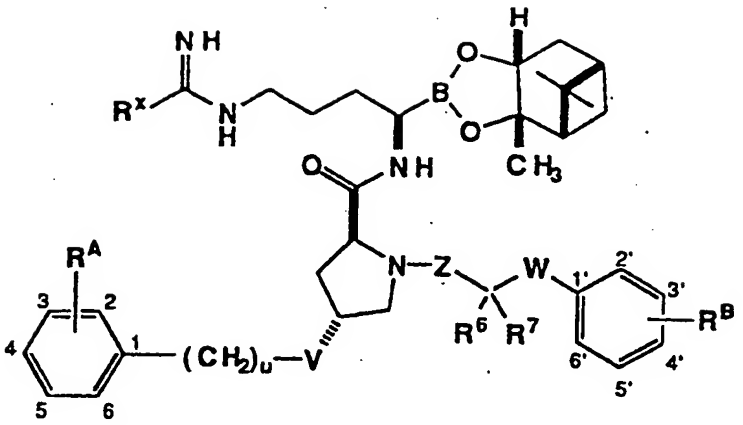
981	2-F	2'-CH_3	H	H	CO	O	CH_2	1	
982	2-F	3'-CH_3	H	H	CO	O	CH_2	1	
983	2-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
984	2-F	2'-F	H	H	CO	O	CH_2	1	
985	2-F	3'-F	H	H	CO	O	CH_2	1	
986	2-F	2'-N	H	H	CO	O	CH_2	1	
987	2-F	3'-N	H	H	CO	O	CH_2	1	
988	3-F	H	H	H	CO	O	CH_2	1	KK
989	3-F	2'-CH_3	H	H	CO	O	CH_2	1	
990	3-F	3'-CH_3	H	H	CO	O	CH_2	1	
991	3-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
992	3-F	2'-F	H	H	CO	O	CH_2	1	
993	3-F	3'-F	H	H	CO	O	CH_2	1	
994	3-F	2'-N	H	H	CO	O	CH_2	1	
995	3-F	3'-N	H	H	CO	O	CH_2	1	
996	3-NH_2	H	H	H	CO	O	CH_2	1	
997	3-NH_2	2'-CH_3	H	H	CO	O	CH_2	1	
998	3-NH_2	3'-CH_3	H	H	CO	O	CH_2	1	
999	3-NH_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1000	3-NH_2	2'-F	H	H	CO	O	CH_2	1	
1001	3-NH_2	3'-F	H	H	CO	O	CH_2	1	
1002	3-NH_2	2'-N	H	H	CO	O	CH_2	1	
1003	3-NH_2	3'-N	H	H	CO	O	CH_2	1	
1004	3-NO_2	H	H	H	CO	O	CH_2	1	
1005	3-NO_2	2'-CH_3	H	H	CO	O	CH_2	1	
1006	3-NO_2	3'-CH_3	H	H	CO	O	CH_2	1	
1007	3-NO_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1008	3-NO_2	2'-F	H	H	CO	O	CH_2	1	
1009	3-NO_2	3'-F	H	H	CO	O	CH_2	1	
1010	3-NO_2	2'-N	H	H	CO	O	CH_2	1	
1011	3-NO_2	3'-N	H	H	CO	O	CH_2	1	
1012	2-N	H	H	H	CO	O	CH_2	1	
1013	2-N	2'-CH_3	H	H	CO	O	CH_2	1	
1014	2-N	3'-CH_3	H	H	CO	O	CH_2	1	
1015	2-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	

1016	2-N	2'-F	H	H	CO	O	CH_2	1
1017	2-N	3'-F	H	H	CO	O	CH_2	1
1018	2-N	2'-N	H	H	CO	O	CH_2	1
1019	2-N	3'-N	H	H	CO	O	CH_2	1
1020	3-N	H	H	H	CO	O	CH_2	1
1021	3-N	2'-CH_3	H	H	CO	O	CH_2	1
1022	3-N	3'-CH_3	H	H	CO	O	CH_2	1
1023	3-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
1024	3-N	2'-F	H	H	CO	O	CH_2	1
1025	3-N	3'-F	H	H	CO	O	CH_2	1
1026	3-N	2'-N	H	H	CO	O	CH_2	1
1027	3-N	3'-N	H	H	CO	O	CH_2	1
1028	4-N	H	H	H	CO	O	CH_2	1
1029	4-N	2'-CH_3	H	H	CO	O	CH_2	1
1030	4-N	3'-CH_3	H	H	CO	O	CH_2	1
1031	4-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
1032	4-N	2'-F	H	H	CO	O	CH_2	1
1033	4-N	3'-F	H	H	CO	O	CH_2	1
1034	4-N	2'-N	H	H	CO	O	CH_2	1
1035	4-N	3'-N	H	H	CO	O	CH_2	1
1036	H	H	H	H	CO	O	O	0
1037	H	H	CH_3	CH_3	CO	S	O	0
1038	H	H	H	H	CO	O	O	1
1039	H	2'- CH_3	H	H	CO	O	O	1
1040	H	3'-CH_3	H	H	CO	O	O	1
1041	H	2', 3'-diCH_3	H	H	CO	O	O	1
1042	H	2'-F	H	H	CO	O	O	1
1043	H	3'-F	H	H	CO	O	O	1
1044	H	2'-N	H	H	CO	O	O	1
1045	H	3'-N	H	H	CO	O	O	1
1046	3-CH_3	H	H	H	CO	O	O	1
1047	3-CH_3	2'-CH_3	H	H	CO	O	O	1
1048	3-CH_3	3'-CH_3	H	H	CO	O	O	1
1049	3-CH_3	2', 3'-diCH_3	H	H	CO	O	O	1
1050	3-CH_3	2'-F	H	H	CO	O	O	1

1051	3-CH_3	3'-F	H	H	CO	O	O	1
1052	3-CH_3	2'-N	H	H	CO	O	O	1
1053	3-CH_3	3'-N	H	H	CO	O	O	1
1054	2-F	H	H	H	CO	O	O	1
1055	2-F	2'-CH_3	H	H	CO	O	O	1
1056	2-F	3'-CH_3	H	H	CO	O	O	1
1057	2-F	2', 3'-diCH_3	H	H	CO	O	O	1
1058	2-F	2'-F	H	H	CO	O	O	1
1059	2-F	3'-F	H	H	CO	O	O	1
1060	2-F	2'-N	H	H	CO	O	O	1
1061	2-F	3'-N	H	H	CO	O	O	1
1062	3-F	H	H	H	CO	O	O	1
1063	3-F	2'-CH_3	H	H	CO	O	O	1
1064	3-F	3'-CH_3	H	H	CO	O	O	1
1065	3-F	2', 3'-diCH_3	H	H	CO	O	O	1
1066	3-F	2'-F	H	H	CO	O	O	1
1067	3-F	3'-F	H	H	CO	O	O	1
1068	3-F	2'-N	H	H	CO	O	O	1
1069	3-F	3'-N	H	H	CO	O	O	1
1070	3-NH_2	H	H	H	CO	O	O	1
1071	3-NH_2	2'-CH_3	H	H	CO	O	O	1
1072	3-NH_2	3'-CH_3	H	H	CO	O	O	1
1073	3-NH_2	2', 3'-diCH_3	H	H	CO	O	O	1
1074	3-NH_2	2'-F	H	H	CO	O	O	1
1075	3-NH_2	3'-F	H	H	CO	O	O	1
1076	3-NH_2	2'-N	H	H	CO	O	O	1
1077	3-NH_2	3'-N	H	H	CO	O	O	1
1078	3-NO_2	H	H	H	CO	O	O	1
1079	3-NO_2	2'-CH_3	H	H	CO	O	O	1
1080	3-NO_2	3'-CH_3	H	H	CO	O	O	1
1081	3-NO_2	2', 3'-diCH_3	H	H	CO	O	O	1
1082	3-NO_2	2'-F	H	H	CO	O	O	1
1083	3-NO_2	3'-F	H	H	CO	O	O	1
1084	3-NO_2	2'-N	H	H	CO	O	O	1
1085	3-NO_2	3'-N	H	H	CO	O	O	1

1086	2-N	H	H	H	CO	O	O	1
1087	2-N	2'-CH_3	H	H	CO	O	O	1
1088	2-N	3'-CH_3	H	H	CO	O	O	1
1089	2-N	2', 3'-diCH_3	H	H	CO	O	O	1
1090	2-N	2'-F	H	H	CO	O	O	1
1091	2-N	3'-F	H	H	CO	O	O	1
1092	2-N	2'-N	H	H	CO	O	O	1
1093	2-N	3'-N	H	H	CO	O	O	1
1094	3-N	H	H	H	CO	O	O	1
1095	3-N	2'-CH_3	H	H	CO	O	O	1
1096	3-N	3'-CH_3	H	H	CO	O	O	1
1097	3-N	2', 3'-diCH_3	H	H	CO	O	O	1
1098	3-N	2'-F	H	H	CO	O	O	1
1099	3-N	3'-F	H	H	CO	O	O	1
1100	3-N	2'-N	H	H	CO	O	O	1
1101	3-N	3'-N	H	H	CO	O	O	1
1102	4-N	H	H	H	CO	O	O	1
1103	4-N	2'-CH_3	H	H	CO	O	O	1
1104	4-N	3'-CH_3	H	H	CO	O	O	1
1105	4-N	2', 3'-diCH_3	H	H	CO	O	O	1
1106	4-N	2'-F	H	H	CO	O	O	1
1107	4-N	3'-F	H	H	CO	O	O	1
1108	4-N	2'-N	H	H	CO	O	O	1
1109	4-N	3'-N	H	H	CO	O	O	1

Table 12



$R^x = H_2N$

ExNo.	R^A	R^B	R^6	R^7	Z	V	W	u	Data
1110	H	H	H	H	C(O)O	O	–	1	
1111	H	H	H	H	CO	O	CH_2	0	
1112	H	H	H	H	CO	S	CH_2	0	
1113	H	H	H	H	CO	O	CH_2	1	LL
1114	H	2'- CH_3	H	H	CO	O	CH_2	1	
1115	H	3'-CH_3	H	H	CO	O	CH_2	1	
1116	H	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1117	H	2'-F	H	H	CO	O	CH_2	1	
1118	H	3'-F	H	H	CO	O	CH_2	1	
1119	H	2'-N	H	H	CO	O	CH_2	1	
1120	H	3'-N	H	H	CO	O	CH_2	1	
1121	3-CH_3	H	H	H	CO	O	CH_2	1	
1122	3-CH_3	2'-CH_3	H	H	CO	O	CH_2	1	
1123	3-CH_3	3'-CH_3	H	H	CO	O	CH_2	1	
1124	3-CH_3	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1125	3-CH_3	2'-F	H	H	CO	O	CH_2	1	
1126	3-CH_3	3'-F	H	H	CO	O	CH_2	1	
1127	3-CH_3	2'-N	H	H	CO	O	CH_2	1	
1128	3-CH_3	3'-N	H	H	CO	O	CH_2	1	
1129	2-F	H	H	H	CO	O	CH_2	1	
1130	2-F	2'-CH_3	H	H	CO	O	CH_2	1	
1131	2-F	3'-CH_3	H	H	CO	O	CH_2	1	

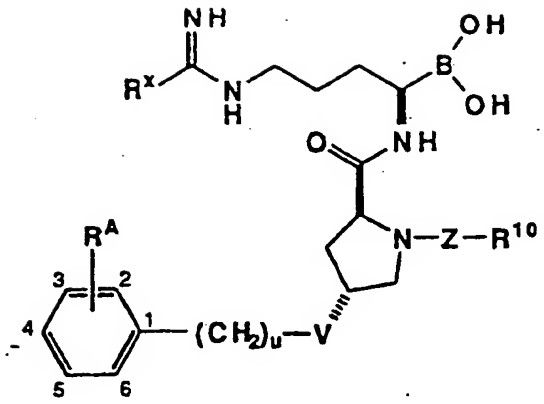
1132	2-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1133	2-F	2'-F	H	H	CO	O	CH_2	1	
1134	2-F	3'-F	H	H	CO	O	CH_2	1	
1135	2-F	2'-N	H	H	CO	O	CH_2	1	
1136	2-F	3'-N	H	H	CO	O	CH_2	1	
1137	3-F	H	H	H	CO	O	CH_2	1	MM
1138	3-F	2'-CH_3	H	H	CO	O	CH_2	1	
1139	3-F	3'-CH_3	H	H	CO	O	CH_2	1	
1140	3-F	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1141	3-F	2'-F	H	H	CO	O	CH_2	1	
1142	3-F	3'-F	H	H	CO	O	CH_2	1	
1143	3-F	2'-N	H	H	CO	O	CH_2	1	
1144	3-F	3'-N	H	H	CO	O	CH_2	1	
1145	3-NH_2	H	H	H	CO	O	CH_2	1	
1146	3-NH_2	2'-CH_3	H	H	CO	O	CH_2	1	
1147	3-NH_2	3'-CH_3	H	H	CO	O	CH_2	1	
1148	3-NH_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1149	3-NH_2	2'-F	H	H	CO	O	CH_2	1	
1150	3-NH_2	3'-F	H	H	CO	O	CH_2	1	
1151	3-NH_2	2'-N	H	H	CO	O	CH_2	1	
1152	3-NH_2	3'-N	H	H	CO	O	CH_2	1	
1153	3-NO_2	H	H	H	CO	O	CH_2	1	
1154	3-NO_2	2'-CH_3	H	H	CO	O	CH_2	1	
1155	3-NO_2	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1156	3-NO_2	2'-F	H	H	CO	O	CH_2	1	
1157	3-NO_2	3'-F	H	H	CO	O	CH_2	1	
1158	3-NO_2	2'-N	H	H	CO	O	CH_2	1	
1159	3-NO_2	3'-N	H	H	CO	O	CH_2	1	
1160	2-N	H	H	H	CO	O	CH_2	1	
1161	2-N	2'-CH_3	H	H	CO	O	CH_2	1	
1162	2-N	3'-CH_3	H	H	CO	O	CH_2	1	
1163	2-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1	
1164	2-N	2'-F	H	H	CO	O	CH_2	1	
1165	2-N	3'-F	H	H	CO	O	CH_2	1	

1166	2-N	2'-N	H	H	CO	O	CH_2	1
1167	2-N	3'-N	H	H	CO	O	CH_2	1
1168	3-N	H	H	H	CO	O	CH_2	1
1169	3-N	2'-CH_3	H	H	CO	O	CH_2	1
1170	3-N	3'-CH_3	H	H	CO	O	CH_2	1
1171	3-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
1172	3-N	2'-F	H	H	CO	O	CH_2	1
1173	3-N	3'-F	H	H	CO	O	CH_2	1
1174	3-N	2'-N	H	H	CO	O	CH_2	1
1175	3-N	3'-N	H	H	CO	O	CH_2	1
1176	4-N	H	H	H	CO	O	CH_2	1
1177	4-N	2'-CH_3	H	H	CO	O	CH_2	1
1178	4-N	3'-CH_3	H	H	CO	O	CH_2	1
1179	4-N	2', 3'-diCH_3	H	H	CO	O	CH_2	1
1180	4-N	2'-F	H	H	CO	O	CH_2	1
1181	4-N	3'-F	H	H	CO	O	CH_2	1
1182	4-N	2'-N	H	H	CO	O	CH_2	1
1183	4-N	3'-N	H	H	CO	O	CH_2	1
1184	H	H	H	H	CO	O	O	0
1185	H	H	CH_3	CH_3	CO	S	O	0
1186	H	H	H	H	CO	O	O	1
1187	H	2'- CH_3	H	H	CO	O	O	1
1188	H	3'-CH_3	H	H	CO	O	O	1
1189	H	2', 3'-diCH_3	H	H	CO	O	O	1
1190	H	2'-F	H	H	CO	O	O	1
1191	H	3'-F	H	H	CO	O	O	1
1192	H	2'-N	H	H	CO	O	O	1
1193	H	3'-N	H	H	CO	O	O	1
1194	3-CH_3	H	H	H	CO	O	O	1
1195	3-CH_3	2'-CH_3	H	H	CO	O	O	1
1196	3-CH_3	3'-CH_3	H	H	CO	O	O	1
1197	3-CH_3	2', 3'-diCH_3	H	H	CO	O	O	1
1198	3-CH_3	2'-F	H	H	CO	O	O	1

1199	3-CH_3	3'-F	H	H	CO	O	O	1
1200	3-CH_3	2'-N	H	H	CO	O	O	1
1201	3-CH_3	3'-N	H	H	CO	O	O	1
1202	2-F	H	H	H	CO	O	O	1
1203	2-F	2'-CH_3	H	H	CO	O	O	1
1204	2-F	3'-CH_3	H	H	CO	O	O	1
1205	2-F	2', 3'-diCH_3	H	H	CO	O	O	1
1206	2-F	2'-F	H	H	CO	O	O	1
1207	2-F	3'-F	H	H	CO	O	O	1
1208	2-F	2'-N	H	H	CO	O	O	1
1209	2-F	3'-N	H	H	CO	O	O	1
1210	3-F	H	H	H	CO	O	O	1
1211	3-F	2'-CH_3	H	H	CO	O	O	1
1212	3-F	3'-CH_3	H	H	CO	O	O	1
1213	3-F	2', 3'-diCH_3	H	H	CO	O	O	1
1214	3-F	2'-F	H	H	CO	O	O	1
1215	3-F	3'-F	H	H	CO	O	O	1
1216	3-F	2'-N	H	H	CO	O	O	1
1217	3-F	3'-N	H	H	CO	O	O	1
1218	3-NH_2	H	H	H	CO	O	O	1
1219	3-NH_2	2'-CH_3	H	H	CO	O	O	1
1220	3-NH_2	3'-CH_3	H	H	CO	O	O	1
1221	3-NH_2	2', 3'-diCH_3	H	H	CO	O	O	1
1222	3-NH_2	2'-F	H	H	CO	O	O	1
1223	3-NH_2	3'-F	H	H	CO	O	O	1
1224	3-NH_2	2'-N	H	H	CO	O	O	1
1225	3-NH_2	3'-N	H	H	CO	O	O	1
1226	3-NO_2	H	H	H	CO	O	O	1
1227	3-NO_2	2'-CH_3	H	H	CO	O	O	1
1228	3-NO_2	3'-CH_3	H	H	CO	O	O	1
1229	3-NO_2	2', 3'-diCH_3	H	H	CO	O	O	1
1230	3-NO_2	2'-F	H	H	CO	O	O	1
1231	3-NO_2	3'-F	H	H	CO	O	O	1
1232	3-NO_2	2'-N	H	H	CO	O	O	1
1233	3-NO_2	3'-N	H	H	CO	O	O	1

1234	2-N	H	H	H	CO	O	O	1
1235	2-N	2'-CH_3	H	H	CO	O	O	1
1236	2-N	3'-CH_3	H	H	CO	O	O	1
1237	2-N	2', 3'-diCH_3	H	H	CO	O	O	1
1238	2-N	2'-F	H	H	CO	O	O	1
1239	2-N	3'-F	H	H	CO	O	O	1
1240	2-N	2'-N	H	H	CO	O	O	1
1241	2-N	3'-N	H	H	CO	O	O	1
1242	3-N	H	H	H	CO	O	O	1
1243	3-N	2'-CH_3	H	H	CO	O	O	1
1244	3-N	3'-CH_3	H	H	CO	O	O	1
1245	3-N	2', 3'-diCH_3	H	H	CO	O	O	1
1246	3-N	2'-F	H	H	CO	O	O	1
1247	3-N	3'-F	H	H	CO	O	O	1
1248	3-N	2'-N	H	H	CO	O	O	1
1249	3-N	3'-N	H	H	CO	O	O	1
1250	4-N	H	H	H	CO	O	O	1
1251	4-N	2'-CH_3	H	H	CO	O	O	1
1252	4-N	3'-CH_3	H	H	CO	O	O	1
1253	4-N	2', 3'-diCH_3	H	H	CO	O	O	1
1254	4-N	2'-F	H	H	CO	O	O	1
1255	4-N	3'-F	H	H	CO	O	O	1
1256	4-N	2'-N	H	H	CO	O	O	1
1257	4-N	3'-N	H	H	CO	O	O	1

Table 13



$R^x = H_2N$

Ex No.	R^A	R^{10}	Z	V	u	Data
1258	H	CH_3	CO	O	0	
1259	3-CH_3	CH_3	CO	O	0	
1260	4-CH_3	CH_3	CO	O	0	
1261	2-F	CH_3	CO	O	0	
1262	3-F	CH_3	CO	O	0	
1263	4-F	CH_3	CO	O	0	
1264	3-NH_2	CH_3	CO	O	0	
1265	4-NH_2	CH_3	CO	O	0	
1266	3-NO_2	CH_3	CO	O	0	
1267	4-NO_2	CH_3	CO	O	0	
1268	3-N	CH_3	CO	O	0	
1269	4-N	CH_3	CO	O	0	
1270	H	CH_3	CO	S	0	
1271	3-CH_3	CH_3	CO	S	0	
1272	4-CH_3	CH_3	CO	S	0	
1273	2-F	CH_3	CO	S	0	
1274	3-F	CH_3	CO	S	0	
1275	4-F	CH_3	CO	S	0	
1276	3-NH_2	CH_3	CO	S	0	
1277	4-NH_2	CH_3	CO	S	0	
1278	3-NO_2	CH_3	CO	S	0	

1279	4-NO_2	CH_3	CO	S	0
1280	3-N	CH_3	CO	S	0
1281	4-N	CH_3	CO	S	0
1282	H	$CH(CH_3)_2$	CO	O	0
1283	3-CH_3	$CH(CH_3)_2$	CO	O	0
1284	4-CH_3	$CH(CH_3)_2$	CO	O	0
1285	2-F	$CH(CH_3)_2$	CO	O	0
1286	3-F	$CH(CH_3)_2$	CO	O	0
1287	4-F	$CH(CH_3)_2$	CO	O	0
1288	3-NH_2	$CH(CH_3)_2$	CO	O	0
1289	4-NH_2	$CH(CH_3)_2$	CO	O	0
1290	3-NO_2	$CH(CH_3)_2$	CO	O	0
1291	4-NO_2	$CH(CH_3)_2$	CO	O	0
1292	3-N	$CH(CH_3)_2$	CO	O	0
1293	4-N	$CH(CH_3)_2$	CO	O	0
1294	H	$CH(CH_3)_2$	CO	S	0
1295	3-CH_3	$CH(CH_3)_2$	CO	S	0
1296	4-CH_3	$CH(CH_3)_2$	CO	S	0
1297	2-F	$CH(CH_3)_2$	CO	S	0
1298	3-F	$CH(CH_3)_2$	CO	S	0
1299	4-F	$CH(CH_3)_2$	CO	S	0
1300	3-NH_2	$CH(CH_3)_2$	CO	S	0
1301	4-NH_2	$CH(CH_3)_2$	CO	S	0
1302	3-NO_2	$CH(CH_3)_2$	CO	S	0
1303	4-NO_2	$CH(CH_3)_2$	CO	S	0
1304	3-N	$CH(CH_3)_2$	CO	S	0
1305	4-N	$CH(CH_3)_2$	CO	S	0
1306	H	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1307	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1308	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1309	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1310	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1311	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1312	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1313	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0

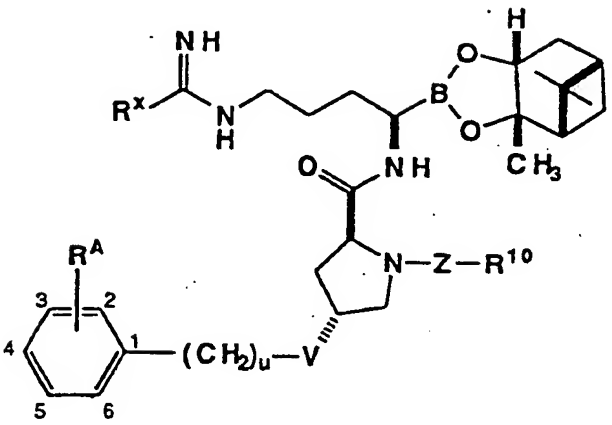
1314	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1315	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1316	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1317	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	0
1318	H	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1319	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1320	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1321	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1322	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1323	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1324	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1325	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1326	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1327	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1328	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1329	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1330	H	CH_3	CO	O	1
1331	3-CH_3	CH_3	CO	O	1
1332	4-CH_3	CH_3	CO	O	1
1333	2-F	CH_3	CO	O	1
1334	3-F	CH_3	CO	O	1
1335	4-F	CH_3	CO	O	1
1336	3-NH_2	CH_3	CO	O	1
1337	4-NH_2	CH_3	CO	O	1
1338	3-NO_2	CH_3	CO	O	1
1339	4-NO_2	CH_3	CO	O	1
1340	3-N	CH_3	CO	O	1
1341	4-N	CH_3	CO	O	1
1342	H	CH_3	CO	S	1
1343	3-CH_3	CH_3	CO	S	1
1344	4-CH_3	CH_3	CO	S	1
1345	2-F	CH_3	CO	S	1
1346	3-F	CH_3	CO	S	1
1347	4-F	CH_3	CO	S	1
1348	3-NH_2	CH_3	CO	S	1

1349	4-NH_2	CH_3	CO	S	1
1350	3-NO_2	CH_3	CO	S	1
1351	4-NO_2	CH_3	CO	S	1
1352	3-N	CH_3	CO	S	1
1353	4-N	CH_3	CO	S	1
1354	H	CH_3	CO	NH	1
1355	3-CH_3	CH_3	CO	NH	1
1356	4-CH_3	CH_3	CO	NH	1
1357	2-F	CH_3	CO	NH	1
1358	3-F	CH_3	CO	NH	1
1359	4-F	CH_3	CO	NH	1
1360	3-NH_2	CH_3	CO	NH	1
1361	4-NH_2	CH_3	CO	NH	1
1362	3-NO_2	CH_3	CO	NH	1
1363	4-NO_2	CH_3	CO	NH	1
1364	3-N	CH_3	CO	NH	1
1365	4-N	CH_3	CO	NH	1
1366	H	$CH(CH_3)_2$	CO	O	1
1367	3-CH_3	$CH(CH_3)_2$	CO	O	1
1368	4-CH_3	$CH(CH_3)_2$	CO	O	1
1369	2-F	$CH(CH_3)_2$	CO	O	1
1370	3-F	$CH(CH_3)_2$	CO	O	1
1371	4-F	$CH(CH_3)_2$	CO	O	1
1372	3-NH_2	$CH(CH_3)_2$	CO	O	1
1373	4-NH_2	$CH(CH_3)_2$	CO	O	1
1374	3-NO_2	$CH(CH_3)_2$	CO	O	1
1375	4-NO_2	$CH(CH_3)_2$	CO	O	1
1376	3-N	$CH(CH_3)_2$	CO	O	1
1377	4-N	$CH(CH_3)_2$	CO	O	1
1378	H	$CH(CH_3)_2$	CO	S	1
1379	3-CH_3	$CH(CH_3)_2$	CO	S	1
1380	4-CH_3	$CH(CH_3)_2$	CO	S	1
1381	2-F	$CH(CH_3)_2$	CO	S	1
1382	3-F	$CH(CH_3)_2$	CO	S	1
1383	4-F	$CH(CH_3)_2$	CO	S	1

1384	3-NH_2	$CH(CH_3)_2$	CO	S	1
1385	4-NH_2	$CH(CH_3)_2$	CO	S	1
1386	3-NO_2	$CH(CH_3)_2$	CO	S	1
1387	4-NO_2	$CH(CH_3)_2$	CO	S	1
1388	3-N	$CH(CH_3)_2$	CO	S	1
1389	4-N	$CH(CH_3)_2$	CO	S	1
1390	H	$CH(CH_3)_2$	CO	NH	1
1391	3-CH_3	$CH(CH_3)_2$	CO	NH	1
1392	4-CH_3	$CH(CH_3)_2$	CO	NH	1
1393	2-F	$CH(CH_3)_2$	CO	NH	1
1394	3-F	$CH(CH_3)_2$	CO	NH	1
1395	4-F	$CH(CH_3)_2$	CO	NH	1
1396	3-NH_2	$CH(CH_3)_2$	CO	NH	1
1397	4-NH_2	$CH(CH_3)_2$	CO	NH	1
1398	3-NO_2	$CH(CH_3)_2$	CO	NH	1
1399	4-NO_2	$CH(CH_3)_2$	CO	NH	1
1400	3-N	$CH(CH_3)_2$	CO	NH	1
1401	4-N	$CH(CH_3)_2$	CO	NH	1
1402	H	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1403	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1404	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1405	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1406	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1407	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1408	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1409	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1410	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1411	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1412	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1413	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1414	H	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1415	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1416	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1417	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1418	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1

1419	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1420	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1421	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1422	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1423	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1424	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1425	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1426	H	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1427	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1428	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1429	2-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1430	3-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1431	4-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1432	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1433	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1434	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1435	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1436	3-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1437	4-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1438	H	$CH_2NH(CH_3)$	CO	O	1
1439	H	$CH_2N(CH_3)CO_2C(CH_3)_3$	CO	O	1

TABLE 14



5

$R^x = H_2N$

Ex No.	R^A	R^{10}	Z	V	u	Data
1440	H	CH_3	CO	O	0	
1441	3-CH_3	CH_3	CO	O	0	
1442	4-CH_3	CH_3	CO	O	0	
1443	2-F	CH_3	CO	O	0	
1444	3-F	CH_3	CO	O	0	
1445	4-F	CH_3	CO	O	0	
1446	3-NH_2	CH_3	CO	O	0	
1447	4-NH_2	CH_3	CO	O	0	
1448	3-NO_2	CH_3	CO	O	0	
1449	4-NO_2	CH_3	CO	O	0	
1450	3-N	CH_3	CO	O	0	
1451	4-N	CH_3	CO	O	0	
1452	H	CH_3	CO	S	0	
1453	3-CH_3	CH_3	CO	S	0	
1454	4-CH_3	CH_3	CO	S	0	
1455	2-F	CH_3	CO	S	0	
1456	3-F	CH_3	CO	S	0	
1457	4-F	CH_3	CO	S	0	
1458	3-NH_2	CH_3	CO	S	0	
1459	4-NH_2	CH_3	CO	S	0	
1460	3-NO_2	CH_3	CO	S	0	
1461	4-NO_2	CH_3	CO	S	0	
1462	3-N	CH_3	CO	S	0	
1463	4-N	CH_3	CO	S	0	
1464	H	$CH(CH_3)_2$	CO	O	0	
1465	3-CH_3	$CH(CH_3)_2$	CO	O	0	
1466	4-CH_3	$CH(CH_3)_2$	CO	O	0	
1467	2-F	$CH(CH_3)_2$	CO	O	0	
1468	3-F	$CH(CH_3)_2$	CO	O	0	
1469	4-F	$CH(CH_3)_2$	CO	O	0	
1470	3-NH_2	$CH(CH_3)_2$	CO	O	0	
1471	4-NH_2	$CH(CH_3)_2$	CO	O	0	

1472	3-NO_2	$CH(CH_3)_2$	CO	O	O
1473	4-NO_2	$CH(CH_3)_2$	CO	O	O
1474	3-N	$CH(CH_3)_2$	CO	O	O
1475	4-N	$CH(CH_3)_2$	CO	O	O
1476	H	$CH(CH_3)_2$	CO	S	O
1477	3-CH_3	$CH(CH_3)_2$	CO	S	O
1478	4-CH_3	$CH(CH_3)_2$	CO	S	O
1479	2-F	$CH(CH_3)_2$	CO	S	O
1480	3-F	$CH(CH_3)_2$	CO	S	O
1481	4-F	$CH(CH_3)_2$	CO	S	O
1482	3-NH_2	$CH(CH_3)_2$	CO	S	O
1483	4-NH_2	$CH(CH_3)_2$	CO	S	O
1484	3-NO_2	$CH(CH_3)_2$	CO	S	O
1485	4-NO_2	$CH(CH_3)_2$	CO	S	O
1486	3-N	$CH(CH_3)_2$	CO	S	O
1487	4-N	$CH(CH_3)_2$	CO	S	O
1488	H	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1489	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1490	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1491	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1492	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1493	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1494	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1495	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1496	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1497	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1498	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1499	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	O
1500	H	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1501	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1502	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1503	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1504	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1505	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	O
1506	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	O

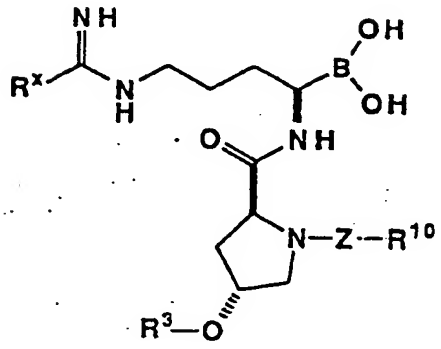
1507	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1508	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1509	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1510	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1511	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	0
1512	H	CH_3	CO	O	1
1513	3-CH_3	CH_3	CO	O	1
1514	4-CH_3	CH_3	CO	O	1
1515	2-F	CH_3	CO	O	1
1516	3-F	CH_3	CO	O	1
1517	4-F	CH_3	CO	O	1
1518	3-NH_2	CH_3	CO	O	1
1519	4-NH_2	CH_3	CO	O	1
1520	3-NO_2	CH_3	CO	O	1
1521	4-NO_2	CH_3	CO	O	1
1522	3-N	CH_3	CO	O	1
1523	4-N	CH_3	CO	O	1
1524	H	CH_3	CO	S	1
1525	3-CH_3	CH_3	CO	S	1
1526	4-CH_3	CH_3	CO	S	1
1527	2-F	CH_3	CO	S	1
1528	3-F	CH_3	CO	S	1
1529	4-F	CH_3	CO	S	1
1530	3-NH_2	CH_3	CO	S	1
1531	4-NH_2	CH_3	CO	S	1
1532	3-NO_2	CH_3	CO	S	1
1533	154-NO_2	CH_3	CO	S	1
1534	3-N	CH_3	CO	S	1
1535	4-N	CH_3	CO	S	1
1536	H	CH_3	CO	NH	1
1537	3-CH_3	CH_3	CO	NH	1
1538	4-CH_3	CH_3	CO	NH	1
1539	2-F	CH_3	CO	NH	1
1540	3-F	CH_3	CO	NH	1
1541	4-F	CH_3	CO	NH	1

1542	3-NH_2	CH_3	CO	NH	1
1543	4-NH_2	CH_3	CO	NH	1
1544	3-NO_2	CH_3	CO	NH	1
1545	4-NO_2	CH_3	CO	NH	1
1546	3-N	CH_3	CO	NH	1
1547	4-N	CH_3	CO	NH	1
1548	H	$CH(CH_3)_2$	CO	O	1
1549	3-CH_3	$CH(CH_3)_2$	CO	O	1
1550	4-CH_3	$CH(CH_3)_2$	CO	O	1
1551	2-F	$CH(CH_3)_2$	CO	O	1
1552	3-F	$CH(CH_3)_2$	CO	O	1
1553	4-F	$CH(CH_3)_2$	CO	O	1
1554	3-NH_2	$CH(CH_3)_2$	CO	O	1
1555	4-NH_2	$CH(CH_3)_2$	CO	O	1
1556	3-NO_2	$CH(CH_3)_2$	CO	O	1
1557	4-NO_2	$CH(CH_3)_2$	CO	O	1
1558	3-N	$CH(CH_3)_2$	CO	O	1
1559	4-N	$CH(CH_3)_2$	CO	O	1
1560	H	$CH(CH_3)_2$	CO	S	1
1561	3-CH_3	$CH(CH_3)_2$	CO	S	1
1562	4-CH_3	$CH(CH_3)_2$	CO	S	1
1563	2-F	$CH(CH_3)_2$	CO	S	1
1564	3-F	$CH(CH_3)_2$	CO	S	1
1565	4-F	$CH(CH_3)_2$	CO	S	1
1566	3-NH_2	$CH(CH_3)_2$	CO	S	1
1567	4-NH_2	$CH(CH_3)_2$	CO	S	1
1568	3-NO_2	$CH(CH_3)_2$	CO	S	1
1569	4-NO_2	$CH(CH_3)_2$	CO	S	1
1570	3-N	$CH(CH_3)_2$	CO	S	1
1571	4-N	$CH(CH_3)_2$	CO	S	1
1572	H	$CH(CH_3)_2$	CO	NH	1
1573	3-CH_3	$CH(CH_3)_2$	CO	NH	1
1574	4-CH_3	$CH(CH_3)_2$	CO	NH	1
1575	2-F	$CH(CH_3)_2$	CO	NH	1
1576	3-F	$CH(CH_3)_2$	CO	NH	1

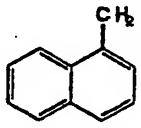
1577	4-F	$CH(CH_3)_2$	CO	NH	1
1578	3-NH_2	$CH(CH_3)_2$	CO	NH	1
1579	4-NH_2	$CH(CH_3)_2$	CO	NH	1
1580	3-NO_2	$CH(CH_3)_2$	CO	NH	1
1581	4-NO_2	$CH(CH_3)_2$	CO	NH	1
1582	3-N	$CH(CH_3)_2$	CO	NH	1
1583	4-N	$CH(CH_3)_2$	CO	NH	1
1584	H	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1585	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1586	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1587	2-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1588	3-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1589	4-F	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1590	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1591	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1592	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1593	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1594	3-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1595	4-N	$CH_2CH_2CH(CH_3)_2$	CO	O	1
1596	H	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1597	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1598	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1599	2-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1600	3-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1601	4-F	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1602	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1603	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1604	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1605	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1606	3-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1607	4-N	$CH_2CH_2CH(CH_3)_2$	CO	S	1
1608	H	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1609	3-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1610	4-CH_3	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1611	2-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1

1612	3-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1613	4-F	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1614	3-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1615	4-NH_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1616	3-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1617	4-NO_2	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1618	3-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1619	4-N	$CH_2CH_2CH(CH_3)_2$	CO	NH	1
1620	H	$CH_2NH(CH_3)$	CO	O	1
1621	H	$CH_2N(CH_3)CO_2C(CH_3)_3$	CO	O	1

Table 15



$R^x = H_2N$, Z=C(=O)

Ex No.	R^3	R^{10}	Data
1622	CH_3	CH_3	
1623	$(H_3C)_3C$	CH_3	
1624		CH_3	

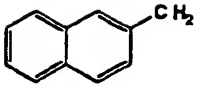
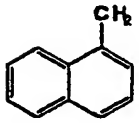
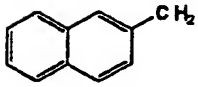
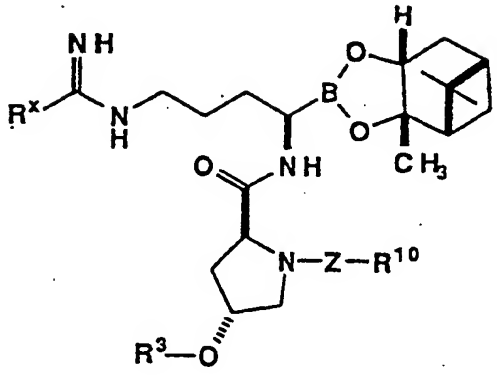
1625		CH_3
1626	CH_3	CH_2CH_2Ph
1627	$(H_3C)_3C$	CH_2CH_2Ph
1628		CH_2CH_2Ph
1629		CH_2CH_2Ph

Table 16



$R^x = H_2N$, Z=C(=O)

Ex No.	R^3	R^{10}	Data
1630	CH_3	CH_3	
1631	$(H_3C)_3C$	CH_3	

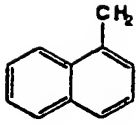
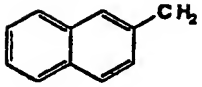
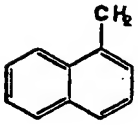
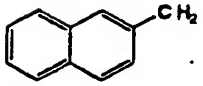
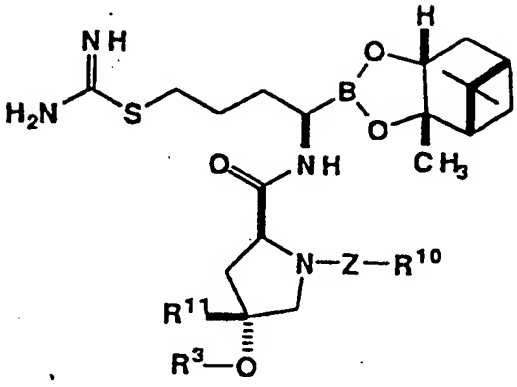
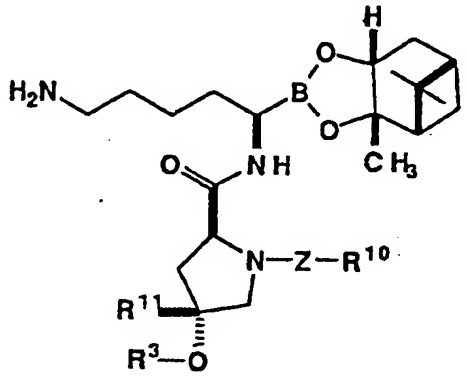
1632		CH_3
1633		CH_3
1634	CH_3	CH_2CH_2Ph
1635	$(H_3C)_3C$	CH_2CH_2Ph
1636		CH_2CH_2Ph
1637		CH_2CH_2Ph

Table 17



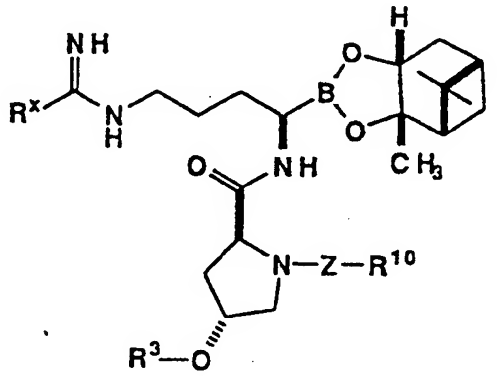
Ex No.	R^3	R^{11}	R^{10}	Z	Data
1638	H	H	CH_2Ph	C(O)O	NN
1639	$PhCH_2$	H	$C(CH_3)_3$	C(O)O	OO
1640	$PhCH_2$	H	CH_3	CO	PP
1641	$PhCH_2$	H	CH_2Ph	C(O)O	QQ

Table 18



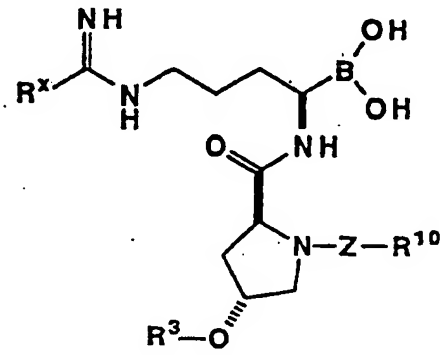
Ex No.	R^3	R^{11}	R^{10}	Z	Data
1642	single bond		CH_2CH_2Ph	CO	RR

TABLE 19



Ex No.	R^3	R^{10}	Z	R^x	Data
1643	CH_2Ph	CH_2CH_2Ph	CO	$NHCH_3$	SS
1644	CH_2Ph	CH_2CH_2Ph	CO	H	TT

Table 20



Ex No.	R^3	R^{10}	Z	R^x	Data
1645	CH_2Ph	CH_2CH_2Ph	CO	$NHCH_3$	UU
1646	CH_2Ph	CH_2CH_2Ph	CO	H	VV

DATA

A HRMS Calcd for $C_{29}H_{42}BN_3O_6$: 540.3245. Found: 540.3248.

B HRMS Calcd for $C_{30}H_{44}BN_3O_6$: 554.3401. Found: 554.3404.

C HRMS Calcd for $C_{31}H_{47}BN_3O_6$: 568.3558. Found: 568.3558.

D HRMS Calcd for $C_{29}H_{42}BN_3O_6$: 540.3245. Found: 540.3248.

E HRMS Calcd for $C_{33}H_{51}BN_3O_6$: 596.3871. Found: 596.3870.

F HRMS Calcd for $C_{33}H_{51}BN_3O_6$: 596.3871. Found: 596.3857.

G HRMS Calcd for $C_{36}H_{48}BN_3O_6$: 630.3714. Found: 630.3709.

H HRMS Calcd for $C_{30}H_{44}BN_3O_7$: 570.3351. Found: 570.3353.

I LRMS Calcd for $C_{30}H_{45}BN_3O_8S$: 618.3. Found: 618.4.

J HRMS Calcd for $C_{31}H_{46}BFN_3O_6$: 586.3464. Found: 586.3456.

K HRMS Calcd for $C_{30}H_{46}BN_4O_6$: 569.3510. Found: 569.3501.

L HRMS Calcd for $C_{38}H_{52}BN_3O_6$: 658.4027. Found: 658.4036.

M HRMS Calcd for $C_{28}H_{39}BN_3O_5$(ethylene glycol ester): 508.2983. Found: 508.2999.

N HRMS Calcd for $C_{27}H_{39}BN_3O_5$(ethylene glycol ester): 522.3139. Found: 522.3123.

O LRMS Calcd for $C_{26}H_{36}BFN_3O_5$ (ethylene glycol ester): 526. Found: 526.

P HRMS Calcd for $C_{35}H_{49}BN_3O_4S$: 618.3537. Found: 618.3537.

Q HRMS Calcd for $C_{36}H_{51}BN_3O_5$: 616.3922. Found: 616.3910.

R HRMS Calcd for $C_{37}H_{53}BN_3O_5$: 630.4078. Found: 630.4060.

S HRMS Calcd for $C_{35}H_{50}BN_4O_5$: 617.3874. Found: 617.3876.

T LRMS Calcd for $C_{36}H_{50}BFN_3O_5$: 634. Found: 634.5.

U LRMS Calcd for $C_{36}H_{52}BN_4O_5$: 631. Found: 631.3.

V HRMS Calcd for $C_{37}H_{53}BN_3O_5$: 630.4078. Found: 630.4071.

W HRMS Calcd for $C_{36}H_{48}BN_3O_6$: 618.3714. Found: 618.3713.

X HRMS Calcd for $C_{36}H_{51}BN_3O_6$: 632.3871. Found: 632.3857.

Y LRMS Calcd for $C_{36}H_{51}BN_4O_4$: 615. Found: 615.5.
Z HRMS Calcd for $C_{29}H_{44}BN_4O_5$: 526.3452. Found: 526.3460.
AA HRMS Calcd for $C_{30}H_{46}BN_3O_5$: 540.3609. Found: 540.3604.
BB HRMS Calcd for $C_{30}H_{47}BN_3O_5$: 540.3609. Found: 540.3620.
CC HRMS Calcd for $C_{31}H_{49}BN_3O_5$: 554.3765. Found: 554.3769.
DD HRMS Calcd for $C_{33}H_{53}BN_4O_7$: 582.4078. Found: 582.4071.
EE HRMS Calcd for $C_{30}H_{48}BN_4O_5$: 555.3718. Found: 555.3735.
FF HRMS Calcd for $C_{35}H_{56}BN_4O_7$: 655.4242. Found: 655.4234.
GG HRMS Calcd for $C_{26}H_{47}BN_3O_5$: 492.3609. Found: 492.3600.
HH HRMS Calcd for $C_{33}H_{47}BN_3O_5$: 576.3609. Found: 576.3593.
II HRMS Calcd for $C_{33}H_{53}BN_3O_5$: 582.4078. Found: 582.4092.
JJ HRMS Calcd for $C_{40}H_{53}BN_3O_5$: 666.4078. Found: 666.4089.
KK LRMS Calcd for $C_{26}H_{36}BFN_5O_5$: 528.3. Found: 528.3.
LL HRMS Calcd for $C_{36}H_{51}BN_5O_5$: 644.3983. Found: 644.3977.
MM LRMS Calcd for $C_{36}H_{50}BFN_5O_5$: 662. Found: 662.
NN HRMS Calcd for $C_{28}H_{42}BN_4O_6S$: 573.2918. Found: 573.2919.
OO HRMS Calcd for $C_{32}H_{50}BN_4O_6S$: 629.3544. Found: 629.3524.
PP HRMS Calcd for $C_{29}H_{42}BN_3O_5S$: 571.3126. Found: 571.3138.
QQ HRMS Calcd for $C_{35}H_{48}BN_4O_6S$: 663.3388. Found: 663.3374.

RR HRMS Calcd for $C_{29}H_{43}BN_3O_5$: 524.3300. Found: 524.3305.

SS LRMS Calcd for $C_{37}H_{53}BN_5O_5$: 653. Found: 658

TT LRMS Calcd for $C_{36}H_{50}BN_4O_5$: 629. Found: 629

UU LRMS Calcd for $C_{27}H_{39}BN_5O_5$: 524. Found: 524

VV LRMS Calcd for $C_{26}H_{36}BN_4O_5$: 495. Found: 495

WW HRMS Calcd for $C_{35}H_{48}BFN_3O_6$: 636.3620. Found: 636.3612.

Utility

The compounds of formula (I) are useful as inhibitors of serine proteases and notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes.

Inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% polyethylene glycol 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the

reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk.

Using the methodology described above, representative compounds of this invention were evaluated and found to exhibit a K_i of less than 1 m*M*, thereby confirming the utility of the compounds of the invention as effective thrombin inhibitors.

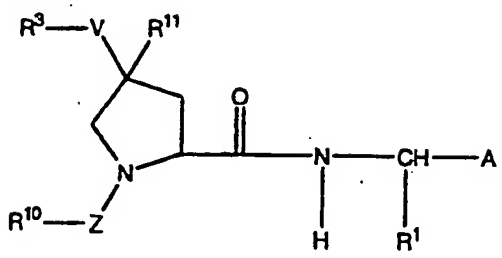
The ability of the compounds to inhibit coagulation was assayed in normal rabbit plasma which was prepared by diluting blood 1:10 with 3.2% aqueous citric acid followed by centrifugation. Bovine thrombin was obtained from Sigma and diluted to 24 NIH units/mL. Plasma (0.2 mL) and buffer (0.05 mL, 0.10 M Tris[hydroxymethyl]-aminomethane hydrochloride, pH 7.4, 0.9% (w/v) sodium chloride, and 2.5 mg/mL bovine serum albumin) containing inhibitor were incubated 3 min at 37 °C in a fibrameter. Reactions were initiated by adding thrombin (0.05 mL) to achieve a final concentration of 4 NIH units/mL. The effectiveness of compounds as anticoagulants is reported as the level of inhibitor required to prolong clotting to that observed for 2 NIH units/mL of thrombin in the absence of inhibitor. In this assay then, better inhibitors require lower concentrations to delay clot formation. Representative compounds of this invention were evaluated and found to be active.

Since the compounds of formula (I) have anti-thrombogenic properties, they may be employed when an anti-thrombogenic agent is indicated, such as for the control of the coagulation of the fibrinolysis system in mammals or they may be added to blood for the purpose of preventing coagulation of the blood due to contact with blood collecting or distribution containers, tubing or apparatus.

Generally, these compounds may be administered orally, parenterally or intravenously to a host to obtain an anti-thrombogenic effect. The dosage of the active compound depends on the mammalian species, body weight, age, and mode of administration as determined by one skilled in the art. In the case of large mammals such as humans, the compounds may be administered alone or in combination with pharmaceutical carriers or diluents at a dose of from 0.02 to 15 mg/kg to obtain the anti-thrombogenic effect, and may be given as a single dose or in divided doses or as a sustained release formulation. Pharmaceutical carriers or diluents are well known and include sugars, starches and water, which may be used to make tablets, capsules, injectable solutions or the like which can serve as suitable dosage forms for administration of the compounds of this invention. Remington's Pharmaceutical Sciences, A. Osol, is a standard reference text which discloses suitable pharmaceutical carriers and dosage forms. The disclosure of this text is hereby incorporated by reference for a more complete teaching of suitable dosage forms for administration of the compounds of this invention.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

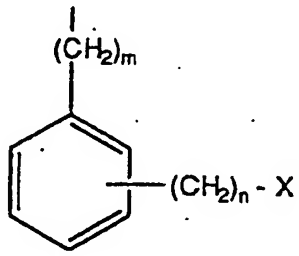
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is

a) $-(C_1-C_{12}$ alkyl$)-X$, or

b) $-(C_2-C_{12}$ alkenyl$)-X$, or

c)



X is

a) halogen,

b) $-CN$,

c) $-NO_2$,

d) $-CF_3$,

e) $-S(O)_pR^2$,

f) $-NHR^2$,

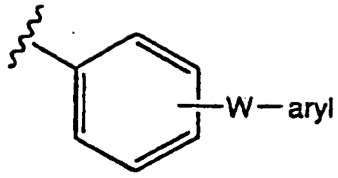
g) $-NHS(O)_pR^2$,

h) $-NHC(=NH)H$,

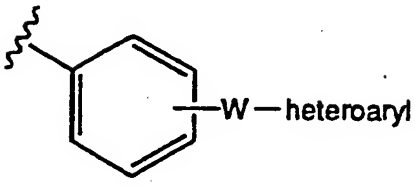
i) -NHC(=NH)NHOH,
j) -NHC(=NH)NHCN,
k) -NHC(=NH)NHR^2,
l) -NHC(=NH)NHC(=O)R^2,
m) -C(=NH)H,
n) -C(=NH)NHR^2,
o) -C(=NH)NHC(=O)R^2,
p) -C(=O)NHR^2,
q) -C(=O)NHC(=O)R^2,
r) -C(=O)OR^2,
s) -OR^2,
t) -OC(=O)R^2,
u) -OC(=O)OR^2,
v) -OC(=O)NHR^2,
w) -OC(=O)NHC(=O)R^2,
x) -SC(=NH)NHR^2;

R^2 is
a) hydrogen,
b) -CF_3
c) C_1-C_4 alkyl,
d) -$(CH_2)_q$-aryl;

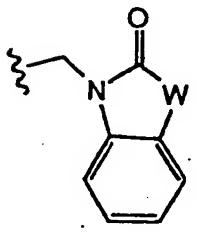
R^3 and R^{10} are independently selected at each occurrence from the group consisting of:
a) hydrogen,
b) halogen,
c) -$(CR^6R^7)_tW(CR^8R^9)_u$-R^9,
d) -$(CR^6R^7)_tW(CR^8R^9)_u$-aryl,
e) -$(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl,
f) -$(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle,
g) -$(CR^6R^7)_tW(CR^8R^9)_u$-adamantyl,
h) -$(CR^6R^7)_tW(CR^8R^9)_u$(C_5-C_7)cycloalkyl,
i)



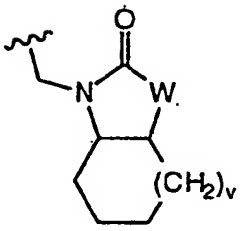
j)



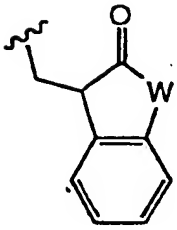
k)



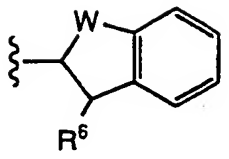
l)



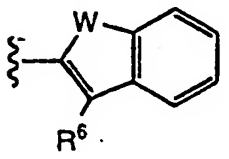
m)



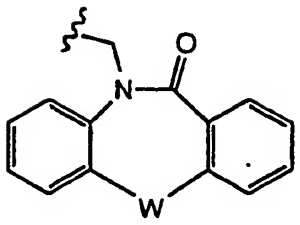
n)



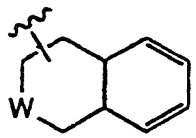
o)



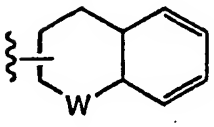
p)



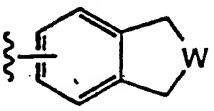
q)



r)



s)



R^3 and R^{10} when taken together form a ring such as:

a) $-(CR^6R^7)_t(CR^8R^9)_u-W-(CR^8R^9)_u(CR^6R^7)_t$;

b) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl-$(CR^8R^9)_uW(CR^6R^7)_t-$;

c) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl-$(CR^8R^9)_uW(CR^6R^7)_t-$;

d) $-(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle-$(CR^8R^9)_uW(CR^6R^7)_t-$;

e) $-(CR^6R^7)_tW(CR^8R^9)_u-W-(CR^8R^9)_uW(CR^6R^7)_t-$;

R^4 and R^5 are independently selected at each occurrence from the group consisting of:

a) hydrogen,

b) C_1-C_4 alkyl,

c) C_1-C_4 alkoxy,

d) C_5-C_7 cycloalkyl,

e) phenyl,

f) benzyl;

R^6, R^7, R^8 and R^9 are independently selected at each occurrence from the group consisting of:

a) hydrogen,

b) C_1-C_6 alkyl,

c) C_1-C_6 alkoxy,

d) C_3-C_8 cycloalkyl,

e) aryl,

f) heterocycle,

g) heteroaryl,

h) -W-aryl,

i) $-(CH_2)_wC(=O)OR^4$,

j) R^6 or R^7 can alternatively be taken together with R^6 or R^7 on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbons, or

k) R^8 or R^9 can alternatively be taken together with R^8 or R^9 on an adjacent carbon atom to form a direct bond,

thereby to form a double or triple bond between said carbons;

R^{11} is

a) hydrogen,
b) C_1-C_4 alkyl,
c) C_1-C_4 thioalkyl,
d) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl,
e) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl,
f) $-(CR^6R^7)_tW(CR^8R^9)_u$-heterocycle, or
g) $-(CR^6R^7)_tW(CR^8R^9)_u-R^9$;

R^{11} and V, when taken together, can also be:

a) keto,
b) $=NR^{10}$,
c) $=C[(CR^6R^7)_tW(CR^8R^9)_uR^2]_2$, or
d) $-(CR^6R^7)_tW(CR^8R^9)_u-W-(CR^6R^7)_tW(CR^8R^9)_u-$

A is

a) $-BY^1Y^2$,
b) $-C(=O)CF_3$,
c) $-C(=O)CF_2CF_3$,
d) $-PO_3H_2$
d) $-C(=O)H$,
e) -C(=O)-1-piperdinyl,
f) $-C(=O)CH_2OCH_2CF_3$,
g) CH_2Cl
h) SO_2F;

Y^1 and Y^2 are

a) -OH,
b) -F,
c) $-NR^4R^5$ -,
d) $-C_1$-C_8 alkoxy, or;

when taken together Y^1 and Y^2 form:

e) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,

f) a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,

g) a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O;

W can be independently selected at each occurence from the group consisting of:

a) $-(CH_2)_x-$,

b) $-C(=O)-$,

c) $-C(=O)O-$,

d) $-C(=O)NR^4-$,

e) $-O-$,

f) $-OC(=O)-$,

g) $-OC(=O)O-$,

h) $-OC(=O)NR^4-$,

i) $-NR^4-$,

j) $-NR^4C(=O)-$,

k) $-NR^4C(=O)O-$,

l) $-NR^4C(=O)NR^5-$,

m) $-NR^4S(O)_p-$

n) $-S(O)_p-$,

o) $-S(O)_pO-$,

p) $-S(O)_pNR^4-$,

q) $-S(O)_pNR^4C(=O)-$,

r) $-S(O)_pNR^4C(=O)NR^5-$;

V is selected from the group consisting of:

a) $-(CH_2)_x-$,

b) $-(CH_2)_xC(=O)-$,
c) $-(CH_2)_xC(=O)O-$,
d) $-C(=O)(CH_2)_x-$,
e) $-O-(CH_2)_x-$,
f) $-O(CH_2)_xC(=O)-$,
g) $-O(CH_2)_xC(=O)O-$,
h) $-O(CH_2)_xC(=O)NR^4-$,
i) $-O(CH_2)_xS(O)_p-$,
j) $-(CH_2)_xS(O)_p-$,
k) $-(CH_2)_xS(O)_pO-$,
l) $-(CH_2)_xS(O)_pNR^4-$,
m) $-(CH_2)_xS(O)_pNR^4C(=O)-$,
n) $-(CH_2)_xS(O)_pNR^4C(=O)NR^5-$,
o) $-(CH_2)_xNR^4-$,
p) $-(CH_2)_xNR^4C(=O)-$,
q) $-(CH_2)_xNR^4C(=O)O-$,
r) $-(CH_2)_xNR^4C(=O)NR^5-$,
s) $-(CH_2)_xNR^5S(O)_p-$;

Z is selected from the group consisiting of:
a) $-(CH_2)_x-$,
b) $-(CH_2)_xC(=O)-$,
c) $-C(=O)(CH_2)_x-$,
d) $-(CH_2)_xC(=O)O-$,
e) $-(CH_2)_xC(=O)NR^4-$,
f) $-(CH_2)_xNR^4-$,
g) $-(CH_2)_xNR^4C(=O)-$,
h) $-(CH_2)_xNR^4C(=O)O-$,
i) $-(CH_2)_xNR^4C(=O)NR^5-$,
j) $-(CH_2)_xNR^4S(O)_p-$,
k) $-(CH_2)_xS(O)_p-$,
l) $-(CH_2)_xS(O)_pNR^4-$,

m can be 0 to 4;

n can be 0 to 4;

p can be 0 to 2

q can be 0 to 4;

r, s, t, u, and v are independently selected at each occurrence from 0 to 6,

w and x are independently selected at each occurence from 0 to 4;

with the following provisos:

(a) when V is $(CH_2)_x$, x cannot be 0 when R^3 is hydrogen;

(b) when Z is $-(CH_2)_xC(=O)-$ and $-C(=O)(CH_2)_x$ and x is 0, R^{10} cannot be halogen;

wherein aryl is defined as phenyl, fluorenyl, biphenyl and naphthyl, which may be unsubstituted or include optional substitution with one to three substituents;

heteroaryl is 2-, or 3-, or 4-pyridyl; 2-or 3-furyl; 2- or 3-benzofuranyl; 2-, or 3-thiophenyl; 2- or 3-benzo[b]thiophenyl; 2-, or 3-, or 4-quinolinyl; 1-, or 3-, or 4-isoquinolinyl; 2- or 3-pyrrolyl; 1- or 2- or 3-indolyl; 2-, or 4-, or 5-oxazolyl; 2-benzoxazolyl ; 2- or 4- or 5-imidazolyl; 1- or 2- benzimidazolyl; 2- or 4- or 5-thiazolyl; 2-benzothiazolyl; 3- or 4- or 5-isoxazolyl; 3- or 4- or 5-pyrazolyl; 3- or 4- or 5-isothiazolyl; 3- or 4-pyridazinyl; 2- or 4- or 5-pyrimidinyl; 2-pyrazinyl; 2-triazinyl; 3- or 4-cinnolinyl; 1-phthalazinyl; 2- or 4-quinazolinyl; or 2-quinoxalinyl ring; said ring(s) may be unsubstitued or

include optional substitution with one to three substituents;

heterocycle is 2- or 3-pyrrolidinyl, a 2-, 3-, or 4-piperidinyl, or a 1-, 3-, or 4-tetrahdroisoquinolinyl, 1-, 2-, or 4-tetrahydroquinoiinyl, 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothiophene, 1-, 2-, 3-, or 4-piperazinyl, and 1-, 2-, 3-, or 4-morpholino; said ring(s) which may be unsubstituted or include optional substitution with one to three substituents;

cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and cyclooctyl;

the substituents which may be attached to the ring(s) above may be independently selected at each occurrence from the group selected from:

halogen, $-CF_3$, C_1-C_4 alkyl, nitro, phenyl, $-(CH_2)_rR^4$, $-(CH_2)_rC(=O)(CH_2)_sR^4$, $-(CH_2)_rC(=O)O(CH_2)_sR^4$, $-(CH_2)_rC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$, methylenedioxy, C_1-C_4 alkoxy, $-CH_2)_rO(CH_2)_sR^4$, $-(CH_2)_rOC(=O)(CH_2)_sR^4$, $-(CH_2)_rOC(=O)O(CH_2)_sR^4$, $-(CH_2)_rOC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rOC(=O)N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rS(O)_p(CH_2)_sR^4$, $-(CH_2)_rS(O)_p(CH_2)_sC(=O)R^4$, $-(CH_2)_rS(O)_p(CH_2)_sC(=O)OR^4$, $-(CH_2)_rS(O)_pN[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rS(O)_pN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][C(=O)O(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4]CON[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4]C(=O)-N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][S(O)_p(CH_2)_sR^5]$.

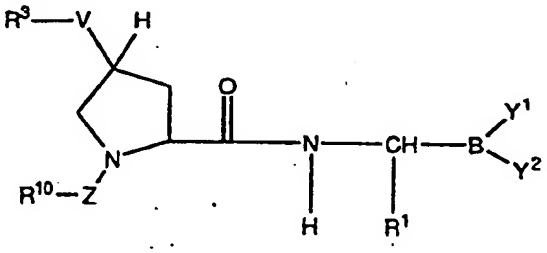
2. A compound of claim 1 wherein:

R^1 is (C_3-C_4 alkyl);

X is selected from the group consisting of:
-NHC(=NH)H, -NHC(=NH)NHR^2, -NH_2 or -SC(=NH)NHR^2;

R^2 is hydrogen or C_1-C_4 alkyl.

3. A compound of claim 2 having formula (Ia) wherein:



(Ia)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is (C_3-C_4 alkyl);

X is selected from the group consisting of:
-NHC(=NH)H, -NHC(=NH)NHR^2, -NH_2 or -SC(=NH)NHR^2;

R^2 is hydrogen or C_1-C_4 alkyl;

R^3 and R^{10} are independently selected at each occurrence from the group consisting of:
a) hydrogen,
b) halogen,

c) $-(CR^6R^7)_tW(CR^8R^9)_u-R^9$

d) $-(CR^6R^7)_tW(CR^8R^9)_u$-aryl

e) $-(CR^6R^7)_tW(CR^8R^9)_u$-heteroaryl;

R^4 and R^5 are independently selected at each occurrence from the group consisting of:

a) hydrogen,

b) C_1-C_4 alkyl,

c) C_1-C_4 alkoxy,

d) phenyl, or

e) benzyl;

R^6, R^7, R^8, R^9 are independently selected at each occurrence from the group consisting of:

a) hydrogen

b) C_1-C_6 alkyl,

c) aryl,

d) $-(CH_2)_wC(=O)OR^4$, or;

Y^1 and Y^2 are

a) -OH,

b) -F,

c) $-NR^4R^5$ -,

d) $-C_1$-C_8 alkoxy, or;

when taken together Y^1 and Y^2 form:

e) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,

f) a cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-3 heteroatoms which can be N, S, or O,

g) a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and,

optionally, 1-3 heteroatoms which can be N, S, or O;

W can be independently selected at each occurrence from the group consisting of:

a) $-(CH_2)_x-$,

b) $-O-$,

c) $-S(O)_p-$,

d) $-NR^4-$,

e) $-NR^4C(=O)-$,

f) $-NR^4C(=O)O-$,

V is selected from the group consisting of:

a) $-(CH_2)_x-$,

b) $-O(CH_2)_x-$,

c) $-O(CH_2)_x(C=O)-$,

d) $-(CH_2)_xS(O)_p-$,

e) $-(CH_2)_xNR^4-$

f) $-(CH_2)_xNR^4C(=O)-$,

g) $-(CH_2)_xNR^4C(=O)O-$;

Z is selected from the group consisiting of:

a) $-(CH_2)_xC(=O)-$,

b) $-C(=O)(CH_2)_x-$,

c) $-(CH_2)_xC(=O)O-$,

p can be 0 or 2;

r can be independently selected at each occurrence from 0 to 3;

s can be independently selected at each occurrence from 0 to 3;

t can be independently selected at each occurrence from 0 to 2;

u can be independently selected at each occurrence from 0 to 2;

w can be independently selected at each occurrence from 0 to 2;

x can be independently selected at each occurrence from 0 to 3;

with the following provisos:

(a) when V is $(CH_2)_x$, x can not be 0 when R^3 is hydrogen;

(b) when Z is $-(CH_2)_xC(=O)-$ and $-C(=O)(CH_2)_x$ and x is 0, R^{10} can not be halogen;

wherein aryl is phenyl, fluorenyl, biphenyl and naphthyl, which may be unsubstituted or include optional substitution with one to three substituents;

heteroaryl is 2-, 3-, or 4-pyridyl; 2-, or 3-furyl; 2-, or 3-thiophenyl; 2-, 3-, or 4-quinolinyl; or 1-, 3-, or 4-isoquinolinyl, which may be unsubstitued or include optional substitution with one to three substituents;

heterocycle is 1-, 3-, or 4-tetrahdroisoquinolinyl, 2- or 3-pyrrolidinyl, and 2-, 3- or 4-piperidinyl, which may be unsubstituted or include optional substitution with one to three substituents;

cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and cyclooctyl;

the substituents which may be attached to the aryl, heteroaryl and heterocycle ring(s) may be independently selected at each occurrence from the group selected from:

halogen, $-CF_3$, C_1-C_4 alkyl, nitro, phenyl, $-(CH_2)_rR^4$, $-(CH_2)_rC(=O)(CH_2)_sR^4$, $-(CH_2)_rC(=O)O(CH_2)_sR^4$, $-(CH_2)_rC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$, methylenedioxy, C_1-C_4 alkoxy, $-CH_2)_rO(CH_2)_sR^4$, $-(CH_2)_rOC(=O)(CH_2)_sR^4$, $-(CH_2)_rOC(=O)O(CH_2)_sR^4$, $-(CH_2)_rOC(=O)N[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rOC(=O)N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rS(O)_p(CH_2)_sR^4$, $-(CH_2)_rS(O)_p(CH_2)_sC(=O)R^4$, $-(CH_2)_rS(O)_p(CH_2)_sC(=O)OR^4$, $-(CH_2)_rS(O)_pN[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rS(O)_pN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][C(=O)O(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4]CON[(CH_2)_sR^4][(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4]C(=O)-N[(CH_2)_sR^4][C(=O)(CH_2)_sR^5]$, $-(CH_2)_rN[(CH_2)_sR^4][S(O)_p(CH_2)_sR^5]$.

4. A compound of claim 3 wherein:

R^3 is independently selected from the group consisting of:

benzyl, phenyl, phenethyl, (3-phenyl)prop-1-yl, (2-methyl-1-phenyl)prop-2-yl, (2-methyl-2-phenyl)prop-1-yl, 1,1-diphenylmethyl, phenoxymethyl, phenylsulfonylmethyl, 2-(*m*-fluorophenyl)ethyl,, 2-(3-pyridyl)ethyl, (*m*-aminophenyl)methyl, (*m*-methylphenyl)methyl, (*p*-methylphenyl)methyl, 1-naphthylmethyl;

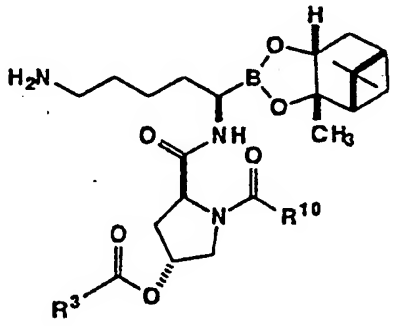
R^{10} is independently selected from the group consisting of:
methyl, t-butoxy, benzyloxy, phenethyl, benzyl, phenoxymethyl, isopropyl, isoamyl, *N*-methyl-*N*-t-butoxycarbonylaminomethyl, *N*-methylaminomethyl, (*m*-methyl)phenethyl, (*m*-fluoro)phenethyl, (*m*-methyl)phenoxymethyl, (3-pyridyl)ethyl;

R^{11} is hydrogen;

V is independently selected from the group consisting of:
O, -OC(=O)-, S, -NH-;

Z is -C(=O)-.

5. A compound of claim 4 of the formula (Ib) selected from the group consisting of:



(Ib)

selected from the list consisting of:

the compound of formula (Ib) wherein R^3 is phenyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 3-phenylprop-1-yl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 1,1-dimethyl-2-phenylethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is 2,2-dimethyl-2-phenylethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is diphenylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenoxymethyl and R^{10} is methyl;

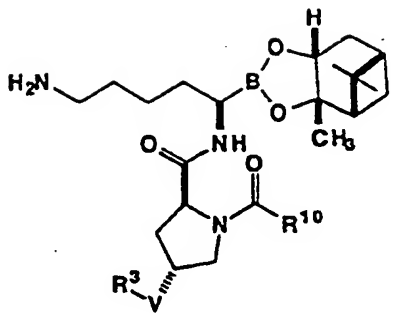
the compound of formula (Ib) wherein R^3 is phenylsulfonylmethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is (*m*-fluorophenyl)ethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is (3-pyridyl)ethyl and R^{10} is methyl;

the compound of formula (Ib) wherein R^3 is phenylethyl and R^{10} is phenethyl.

6. A compound of claim 4 of the formula (Ic) selected from the group consisting of:



(Ic)

selected from the list consisting of:

the compound of formula (Ic) wherein V is sulfur, R^3 is phenyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is 3-phenylpropyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-methyl)phenoxymethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-fluoro)phenoxymethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-methylphenyl)ethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-fluorophenyl)ethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenoxymethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (*m*-fluorophenyl)methyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is amino, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is 2-propyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is isoamyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (*m*-methylphenyl)methyl and R^{10} is methyl;

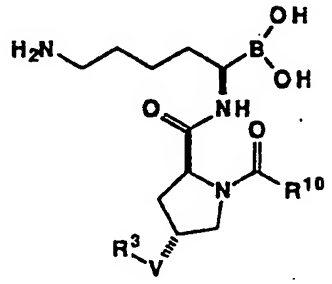
the compound of formula (Ic) wherein V is oxygen, R^3 is (*p*-methylphenyl)methyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is (1-naphthyl)methyl and R^{10} is methyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is *N*-methyl-*N*-*t*-butoxycarbonylaminomethyl;

the compound of formula (Ic) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is *N*-methylaminomethyl.

7. A compound of claim 4 of the formula (Id) selected from the group consisting of:



(Ic)

selected from the list consisting of:

the compound of formula (Id) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is phenethyl;

the compound of formula (Id) wherein V is oxygen, R^3 is (*m*-fluorophenyl)methyl and R^{10} is phenethyl.

the compound of formula (Id) wherein V is oxygen, R^3 is phenylmethyl and R^{10} is (*m*-methyl)phenethyl;

8. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 1.

9. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 2.

10. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 3.

11. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 4.

12. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 5.

13. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 6.

14. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a therapeutically effective amount of a compound of claim 7.

15. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 1.

16. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 2.

17. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 3.

18. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 4.

19. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 5.

20. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 6.

21. A method of treating a physiological disorder in a warm blooded animal catalyzed by serine protease enzymes comprising administering to an animal in need of such treatment an effective amount of a compound of claim 7.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 94/11049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F5/02 A61K31/69 C07K5/062 C07D207/16 C07F9/572
A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 293 881 (E.I. DU PONT DE NEMOURS AND CO.) 7 December 1988 cited in the application see the whole document	1-21
Y	EP,A,0 504 064 (MERRELL DOW PHARMACEUTICALS INC.) 16 September 1992 see the whole document	1-21
Y	EP,A,0 471 651 (SANDOZ LTD.) 19 February 1992 cited in the application see the whole document	1-21
Y	WO,A,92 07869 (THROMBOSIS RESEARCH INSTITUTE) 14 May 1992 cited in the application see the whole document	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1994	-2. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US 94/11049

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